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(54) Title: FELINE IMMUNODEFICIENCY VIRUS CLONE JSY3

(57) Abstract

A full length genomic clone (JSY3) of FIV-$NCSU_1$ was isolated and sequenced. The JSY3 molecular clone retains in the *in vivo* biological characteristics of the parent virus, including the ability to cause a significant inversion of the CD4+/CD8+ ratio by six weeks post infection.

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FELINE IMMUNODEFICIENCY VIRUS CLONE JSY3

This invention was made with government support under Public Health Service grant NO1 AI 35515 from the NIAIDS-DAIDS. The government may have certain rights to this invention.

Field of the Invention

This invention concerns a Feline Immunodeficiency Virus molecular clone which is highly infectious *in vivo* and which produces immunodeficiency in infected subjects.

Background of the Invention

Feline immunodeficiency virus (FIV), a lentivirus of cats, is associated with feline acquired immunodeficiency syndrome (AIDS). *See* N. Pedersen et al., *Science* 235: 790 (1987). Disorders associated with FIV infection include chronic gingivitis/stomatitis, chronic upper respiratory infections, chronic enteritis, and recurrent ocular disease. *See* R. English et al., *J. Am. Vet. Med. Assoc.* 196: 1116 (1990); N. Pedersen et al., *Vet. Immunol. Immunopathol.* 21: 111 (1989); J. Yamamoto et al., *J. Am. Vet. Med. Assoc.* 194: 213 (1989). What is known to date of the pathogenesis of FIV infection suggests that it is a valuable animal model for other retroviral diseases, such as human immunodeficiency virus-1 (HIV-1) infection. HIV-1 and FIV belong to the lentivirus subfamily of retroviruses, have similar morphology, protein composition, and Mg^{2+}-dependency of their reverse transcriptases (RT). *See* N. Pedersen et al., *Science* 235: 790 (1987); N.

Pedersen et al., *Vet. Immunol. Immunopathol.* 21:111 (1989). They both display tropism for T lymphocytes and monocytes and are capable of inducing these cells to form syncytia. *See* D. Brunner and N. Pedersen, *J. Virol.* 63: 5483 (1989); M. Gardner and P. Luciw, *FASEB Journal* 3: 2593 (1989). HIV-1 displays a particular tropism for $CD4^+$ lymphocytes, which leads to their gradual depletion and an inversion of the $CD4^+$:$CD8^+$ ratio. *See* A. Dalgleish et al., *Nature* 312: 763 (1984). The pathogenesis of HIV-1 infection has been attributed to virus-induced reduction of $CD4^+$ lymphocyte numbers and functions, resulting in decreased immune responsiveness and subsequent severe secondary infections. *See* M. McChesney and M. Oldstone, *Ad. Immunol.* 45: 335 (1989).

Yamamoto et al. studied the early events in the pathogenesis of FIV in kittens. *See* J. Yamamoto et al., *Am. J. Vet. Res.* 49: 1246 (1988). These kittens developed an acute infection syndrome similar to that seen in HIV-1, including low grade fever and transient generalized lymphadenopathy. More recent studies by Ackley et al., *J. Virol.* 64: 5652 (1990), utilized monoclonal antibodies directed against feline $CD4^+$ and $CD8^+$ homologues and Pan T cells to analyze lymphocyte profiles in SPF cats experimentally infected with FIV. These authors reported that a significant inversion of the $CD4^+$:$CD8^+$ ratios occurred only in cats infected for 18 months or more. The inversion was associated with a decrease in absolute number of $CD4^+$ cells and an increase in $CD8^+$ cells.

A panel of monoclonal antibodies specific for feline T cell subsets (M. Tompkins et al., *Vet. Immunol. Immunopathol.* 26: 305 (1990)) has been used to analyze T cell numbers and profiles in cats naturally infected with FIV. *See* C. Novotney et al., *AIDS* 4: 1213 (1990). Similar to the observation of Ackley et al. *supra*, cats naturally infected with FIV have an inverted $CD4^+$:$CD8^+$ ratio characterized by a selective reduction in $CD4^+$ cells.

Summary of the Invention

A first aspect of the present invention is an isolated feline immunodeficiency virus (FIV) having all of the identifying characteristics of FIV clone JSY3.

A further aspect of the present invention is an isolated feline immunodeficiency virus (FIV) whose proviral DNA comprises a DNA sequence selected from SEQ ID NO:1 and sequences which vary from SEQ ID NO:1 due to the degeneracy of the genetic code.

A further aspect of the present invention is a biologically pure culture of host cells containing feline immunodeficiency virus as described above.

A further aspect of the present invention is isolated DNA comprising a DNA sequence selected from SEQ ID NO:1 and sequences which vary from SEQ ID NO:1 due to the degeneracy of the genetic code; vectors containing such DNA; and host cells containing and capable of expressing such vectors.

A further aspect of the present invention is isolated DNA comprising a DNA sequence selected from (a) SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:19, and (b) sequences which vary from those of (a) above due to the degeneracy of the genetic code; vectors containing such DNA; and host cells containing and capable of expressing such vectors.

A further aspect of the present invention is a polypeptide having a sequence selected from SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:15, SEQ ID NO:17, and SEQ ID NO:20.

A further aspect of the present invention is a specific pathogen free (SPF) cat infected with feline immunodeficiency virus clone JSY3.

Brief Description of the Drawings

Figure 1A - 10 provide the DNA sequence of the FIV-NCSU$_1$ insert of the lambda clone. The first three nucleotides are part of the lambda vector DNA sequence; the FIV

proviral DNA sequence begins with the fourth nucleotide of Figure 1A. The *gag* region (and the p15, p25, p24a and p10 regions therein), the *pol* region (and two open reading frames (orf) therein, and the *env* region (and the transmembrane (TM) protein therein) are indicated.

Figure 2A - 2H aligns the group specific antigen (*gag*) open reading frame of the FIV $NCSU_1$ JSY3 molecular clone with those of six known FIV strains: FIV PPR, FIV Z1, FIV CG, FIV 14, FIV TM1 and FIV TM2.

Figure 3A - 3O aligns the envelope protein sequence of FIV $NCSU_1$ JSY3 molecular clone with those of five known FIV strains: FIV 14, FIV Z1, FIV CG, FIV 19k, and FIV PPR.

Figure 4 is a schematic of the strategy used for the molecular cloning of the FIV JSY3 full-length genome, beginning with total cellular DNA from FCD4E cells directly infected with FIV-$NCSU_1$.

Detailed Description of the Invention

A major limitation of the FIV model for the study of retroviral infection is the unavailability of molecular clones that retain the pathogenic characteristics of the wild-type viruses. Genetically homogeneous molecular clones of FIV that retain the biological and disease-causing properties of the pathogenic wild-type populations are useful for understanding the molecular basis for determinants of FIV pathogenesis, treatment of FIV, and the relevance of FIV to other retroviral infections.

The FIV molecular clones FIV-14 (Olmsted et al., *PNAS USA* 86:2448 (1989)), FIV-pF34 of FIV-Petaluma (Sparger et al., *Virology* 205:546 (1994)), FIV-pPPR of FIV-PPR (Sparger et al., *Virology* 205:546 (1994)), pFTM191CG of FIV-TM1 (Miyazawa et al., *J. Virol.* 65:1572 (1991)), and 19K1 of FIV Amsterdam-19 (Siebelink et al., *J. Virol.* 66:1091 (1992)), have been reported to be infectious *in vivo* as determined by seroconversion, cell-associated virus, and the presence of FIV provirus. No clone has been reported as pathogenic to the extent that it causes immunodeficiency

and increased susceptibility to secondary opportunistic infections.

An isolate of FIV (FIV-NCSU$_1$) that is pathogenic *in vivo*, as measured by a severe loss of CD4+ cells and development of secondary infections, severe wasting, neurological disease, and B-cell lymphomas, has been described recently (English et al., *J. Infect. Dis.* 170:543 (1994)). Davidson et al. (*Am. J. Pathol.* 143:1486 (1993)) were able to demonstrate that FIV-NCSU$_1$ causes a relatively early and profound state of immunodeficiency, as measured by loss of resistance to challenge with a *Toxoplasma gondii* strain with a low level of virulence. This dual FIV-*T. gondii* infection provides a model with which to determine the ability of FIV isolates as well as molecular clones of FIV to cause immunodeficiency.

A full length FIV-NCSU$_1$ genome (JSY3) was cloned directly from FIV-NCSU$_1$ infected feline CD4+ lymphocyte (FCD4E) genomic DNA and identified by polymerase chain reaction (PCR) amplification with 5'-LTR, *gag*, *env*, 3'-LTR primer sets. Supernatant collected from FCD4E cells cocultured with JSY3-transfected Crandell feline kidney (CrFK) cells was used as inoculum. Cell-free JSY3 virus was cytopathogenic for FCD4E lymphocytes, but did not infect CrFK cells *in vitro*. To determine *in vivo* infectivity and pathogenesis, 6 young adult SPF cats were inoculated with cell-free JSY3 virus. Provirus was detected at 2 wk post-infection, and was still detectable at 25 weeks post infection as determined by *gag* region PCR/Southern blot analysis of peripheral blood mononuclear cell (PBMC) lysates. Infectious virus was recovered from PBMC at six weeks and 25 weeks post infection, and antibody response to FIV was detected by four weeks post infection. In the acute phase of infection, JSY3 provirus was found only in the CD4+ lymphocyte subset; however, by 14 weeks post invention the greatest provirus burden was detected in B lymphocytes. All six cats were panleukopenic at two weeks post infection, CD4+:CD8+ ratios were inverted by six

weeks post-infection, and 5/6 cats developed lymphadenopathy by ten weeks post infection. To determine if the JSY3 molecular clone caused immunodeficiency similar to the parent wild-type FIV-$NCSU_1$, the cats were challenged with the low virulence ME49 strain of *Toxoplasma gondii* (*T. gondii*) at 29 weeks post infection. Five of six cats developed acute respiratory distress and required euthanasia. Histopathologic examination of the severely affected cats revealed generalized inflammatory reactions and the presence of *T. gondii* tachyzoites in multiple tissues. None of the six age- and sex-matched SPF cats inoculated with only *T. gondii* developed clinical disease. These results indicate that the pathogenesis of the molecularly cloned $NCSU_1$ JSY3 isolate is similar to the wild-type FIV-$NCSU_1$ and induces immunodeficiency in cats.

The JSY3 molecular clone retains the essential *in vitro* and *in vivo* biological characteristics of the parent virus. This clone was obtained from an EMBL3 lambda phage library made from FCD4E cells, and the intact genomic structure was confirmed by PCR comparison with the FIV-pPPR molecular clone. The JSY3 molecular clone recovered was highly infectious for PBMCs and FCD4E cells but failed to infect CrFK cells, thus retaining the tropism of the parent FIV-$NCSU_1$ virus. Miyazawa et al. (Miyazawa et al., *J. Virol.* 65:1572 (1991)) and Siebelink et al. (Siebelink et al., *J. Virol.* 66:1091 (1992)) reported that CD4+ lymphoblastoid cell line MYA-1 cell-derived or bone marrow-derived molecular clones of FIV recovered from transfected CrFK cells failed to reinfect CrFK but retained their tropism for PBMC and CD4+ cell cultures. Similarly, the PBMC-derived molecular clone FIV-pPPR replicated efficiently in PBMCs but did not infect adherent cells such as CrFK or G355-5 cells (Phillips et al., *J. Virol.* 64:4605 (1990)), whereas the FIV-p34 clone, derived from the CrFK-adapted Petaluma isolate, replicated efficiently in feline adherent cells, including CrFK cells, but inefficiently in PBMCs (Sparger et al., *Virology* 205:546 (1994)).

The JSY3 clone retains the *in vivo* biological characteristics of the parent $NCSU_1$ virus. Both viruses caused a significant inversion of the CD4+/CD8+ ratio by six weeks post infection. As reported previously for a number of biological isolates of FIV (Ackley et al., *J. Virol.* 64:5652 (1990); Torten et al., *J. Virol.* 65:2225 (1991); Willett et al., *Immunology*, 78:1 (1993)), including the $NCSU_1$ isolate (English et al., *J. Infect. Dis.* 170:543 (1994); Tompkins et al., *J. Am. Vet. Med. Assoc.* 199:1311 (1991)), the inverted CD4+/CD8+ ratio caused by the JSY3 clone was the result of a loss of CD4+ lymphocytes and an increase in CD8+ lymphocytes. Consistent with the $NCSU_1$ biological isolate, the JSY3 molecular clone caused a strong antibody response to *gag* and *env* antigens, and PBMCs had a high burden of FIV provirus during the acute-stage infection.

The JSY3 clone exhibited a pattern similar to the parent FIV-$NCSU_1$ (English et al., *J. Virol.* 67:5175 (1993)) of high provirus burden in CD4+ cells during acute-stage infection, followed by a gradual shift to a panlymphotropic pattern during the transition from the acute to the asymptomatic stage of infection.

Derivation of molecular clones of viruses from *in vitro* culture systems poses the risk of selection of some viral genotypes over others (*see* Dahl et al., *J. Virol.* 61:1602 (1987; Evans et al., *J. Immunol.* 138:3415 (1987); Meyerhans et al., *Cell* 58:901 (1989)), or introduction of modifications in cultured virus, (*see* Hirsch et al., *Nature* 341:767 (1989); Kodama et al., *J. Virol.* 63:4709 (1989)). For FIV, Sparger et al. (Sparger et al., *Virology* 205:546 (1994)) reported that the pF34 clone derived from the CrFK-adapted Petaluma isolate is less pathogenic than the parent Petaluma virus isolated from PBMCs. In contrast the FIV-pPPR molecular clone derived from PPR-infected PBMCs and the biological parent PPR isolate show similar pathogenicities, including virus burden in PBMCs and reduced CD4+/CD8+ ratios (Sparger et al., *Virology* 205:546

(1994)). The JSY3 molecular clone also retains the essential biological characteristics of the parent isolate. This may be largely because the risk of culture-related artifacts was minimized by isolating FIV-$NCSU_1$ genomic DNA from FIV-inoculated CD4+ lymphocytes (FCD4E cells). The FCD4E cells used had been in laboratory culture for several years, but remained interleukin-2 dependent and appeared to express a normal rather than a transformed phenotype and thus represent as near as possible *in vitro* the primary *in vivo* target of FIV.

The value of a molecular clone for studies of pathogenesis depends on its ability to replicate the disease caused by its biological parent virus. The $NCSU_1$ isolate of FIV causes an acute-stage clinical disease characterized by fever and lymphadenopathy that is transient and resolves as the infection progresses to the clinically asymptomatic stage of infection. The JSY3 acute-stage infection was also characterized by a fever and lymphadenopathy that was followed by a clinically asymptomatic stage.

Davidson et al. (*Am. J. Pathol.* 143:1486 (1993)) reported that cats infected with FIV-$NCSU_1$ become highly susceptible to a normally avirulent strain of *T. gondii* as early as 18 weeks post-FIV infection. This dual FIV-*T. gondii* infection was utilized herein to determine if infection with clone JSY3 also caused an immunodeficiency early in the asymptomatic stage of infection; *T. gondii* infection of cats with prior JSY3 infection resulted in severe clinical infection as described below.

The present observations indicate that the JSY3 molecular clone causes a major impairment in the immune response, resulting in enhanced susceptibility to secondary infection by *T. gondii*. Thus, JSY3 possesses all of the essential biological characteristics of the parent $NCSU_1$ isolate, including induction of immunodeficiency.

A. The JSY3 Genome

The DNA sequence of the JSY3 provirus clone of FIV-$NCSU_1$ is provided in **Figure 1**, with the group specific antigen (*gag*), polymerase (*pol*), and envelope protein (*env*) regions marked. The JSY3 proviral DNA sequence consists of 9471 base pairs (SEQ ID NO:1).

The coding region of *gag* is nucleotides 631-1980 of SEQ ID NO:1 (SEQ ID NO:4) and encodes a 450 amino acid product (SEQ ID NO:2).

The coding region for the p15 protein is nucleotides 631-1035 of SEQ ID NO:1 (SEQ ID NO:5), with a polypeptide product of 135 amino acids (SEQ ID NO:6).

The coding region for the p25 protein is nucleotides 1036-1704 of SEQ ID NO:1 (SEQ ID NO:7), with a polypeptide product of 223 amino acids (SEQ ID NO:8).

The coding region for the p24a protein is nucleotides 1264-1305 of SEQ ID NO:1 (SEQ ID NO:9), with a polypeptide product of 14 amino acids (SEQ ID NO:10).

The coding region for the p10 protein is nucleotides 1717-1980 of SEQ ID NO:1 (SEQ ID NO:11), with a polypeptide product of 88 amino acids (SEQ ID NO:12).

The coding region of *pol* is amino acids 2151-5991 of SEQ ID NO:1 (SEQ ID NO:13). Two open reading frames (orfs) are found in the *pol* region. Orf 1 is nucleotides 2151-5243 of SEQ ID NO:1 (SEQ ID NO:14), encoding a product of 1031 amino acids (SEQ ID NO:15); Orf 2 is nucleotides 5239-5991 of SEQ ID NO:1 (SEQ ID NO:16) and encodes a product of 251 amino acids (SEQ ID NO:17).

The *env* coding region is nucleotides 6269-8824 of SEQ ID NO:1 (SEQ ID NO:18) and encodes a protein of 852 amino acids (SEQ ID NO:3). The transmembrane (TM) peptide is encoded by nucleotides 8339-8374 of SEQ ID NO:1 (SEQ ID NO:19), and is 12 amino acids in length (SEQ ID NO:20).

Figure 2 aligns the *gag* open reading frames of the JSY3 clone of $NCSU_1$ (FIV-NCSU), FIV PPR, FIV Z1, FIV CG, FIV 14, FIV TM1, and FIV TM2. **Figure 3** aligns the whole envelope protein sequence of clone JSY3 of $NCSU_1$ with FIV 14, FIV Z1,

FIV CG, FIV 19k, and FIV PPR.

Amino acid sequences disclosed herein are presented in the amino to carboxy direction, from left to right. The amino and carboxy groups are not presented in the sequence. Nucleotide sequences are presented herein by single strand only, in the 5′ to 3′ direction, from left to right. Nucleotides and amino acids are represented herein in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission, or (for amino acids) by three letter code in accordance with 37 C.F.R. §1.822 and established usage. *See, e.g.* PatentIn User Manual, 99-102 (Nov. 1990) (U.S. Patent and Trademark Office, Office of the Assistant Commissioner for Patents, Washington D.C. 20231); U.S. Patent No. 4,871,670 to Hudson et al. at Col. 3, lines 20-43 (applicants specifically intend that the disclosure of this and all patent references cited herein are to be incorporated herein by reference).

Aspects of the present invention are achieved by a viral clone having the DNA sequence as provided herein for Feline Immunodeficiency Virus clone JSY3.

B. Identification of Antigenic Fragments

Antigenic fragments of the present invention are peptides which contain at least one epitope (antibody binding site) which binds antibodies which bind to the FIV clone of the present invention. The antigenic fragments are preferably capable of inducing an immune response when administered to a feline subject, as discussed in greater detail below. In addition, the antigenic fragments preferably bind antibodies which do not bind to prior FIV isolates. DNA encoding such antigenic fragments may be used to transform host cells to thereby produce such antigenic fragments, as explained in greater detail below.

Antigenic fragments may be identified by a variety of means. A protein from FIV clone JSY3 (such as the envelope protein, the gag open reading frame product, or a gag peptide such as p10, p15, p24a or p25) may be fragmented

with a protease, and the fragments tested to determine whether or not a fragment reacts with antiserum against the protein. *See, e.g.*, J. Robinson et al., *Mol. Cell Biochem.* **21**, 23-32 (1978). Another technique is to synthesize peptides which are fragments of the entire protein, and determine whether the individual fragments are recognized by neutralizing antibodies against the protein. *See, e.g.*, J. Gerin et al., *in Vaccines 85: Molecular and Chemical Basis of Resistance to Parasitic, Bacterial and Viral Diseases*, 235-239 (Lerner et al., eds. 1985). Still another method useful for obtaining immunogenic fragments of a protein is by isolation and identification of monoclonal escape mutants. In this strategy, FIV is produced in the presence of a monoclonal antibody to the virus. The only virus which can grow under these conditions are those with a mutation in the nucleotide sequence which codes for an epitope to which the monoclonal antibody binds. A mutant virus which grows under these conditions is referred to as the "monoclonal escape mutant." The monoclonal escape mutant is then sequenced and the mutant sequence compared with the nucleotide sequence of clone JSY3 to find the specific location of the mutation. The mutation is located in a region which codes for a protective epitope, or an "immunogenic fragment." *See, e.g.*, J. Lopez et al., Location of a Highly Conserved Neutralizing Epitope in the F Glycoprotein of Human Respiratory Syncytial Virus, *J. Virol.* 64, 927 (1990).

C. Genetic Engineering Techniques

The production of DNA, vectors, transformed host cells, FIV virus, proteins, and protein fragments of the present invention by genetic engineering techniques can be carried out in accordance with methods known in the art. *See, e.g.*, U.S. Patent No. 4,761,371 to Bell et al. at Col. 6 line 3 to Col. 9 line 65; U.S. Patent No. 4,877,729 to Clark et al. at Col. 4 line 38 to Col. 7 line 6; U.S. Patent No. 4,912,038 to Schilling at Col. 3 line 26 to Col.

14 line 12; and U.S. Patent No. 4,879,224 to Wallner at Col. 6 line 8 to Col. 8 line 59.

Vectors are replicable DNA constructs used to either amplify or express DNA of the present invention. An expression vector is a replicable DNA construct in which DNA of the present invention is operably linked to control sequences capable of expressing that DNA in a suitable host. Generally, control sequences include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences which control the termination of transcription and translation. Suitable vectors include plasmids, viruses (e.g., vaccinia virus, adenovirus, baculovirus, cytomegalovirus), phage, and integratable DNA fragments (i.e., fragments integratable into the host genome by recombination).

DNA regions are operably linked or operably associated when they are functionally related to each other. For example, a promoter is operably linked to a coding sequence if it controls the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to permit translation.

Transformed host cells are cells which have been transformed or transfected with vectors as described above. Transformed host cells ordinarily express the DNA of the present invention. As used herein, host cells containing the FIV clone JSY3 refer to isolated cells (or cultures of such cells) naturally infected with JSY3, including cells containing the JSY3 proviral DNA integrated into cellular DNA. Suitable host cells include prokaryote, yeast or higher eukaryotic cells such as mammalian cells and insect cells.

Prokaryote host cells include gram negative or gram positive organisms, for example *Escherichia coli* (*E. coli*) or Bacilli. Exemplary host cells are E. coli W3110 (ATCC 27,325), E. coli B, E. coli X1776 (ATCC 31,537), E. coli 294 (ATCC 31,446). A broad variety of suitable prokaryotic

and microbial vectors are available. E. coli is typically transformed using pBR322. Promoters most commonly used in recombinant microbial expression vectors include the β-lactamase (penicillinase) and lactose promoter systems (Chang et al., *Nature* 275:615 (1978); and Goeddel et al., *Nature* 281:544 (1979)), a tryptophan (trp) promoter system (Goeddel et al., *Nucleic Acids Res*. 8:4057 (1980) and EPO App. Publ. No. 36,776) and the tac promoter (H. De Boer et al., *Proc. Natl. Acad. Sci. USA* 80:21 (1983)). The promoter and Shine-Dalgarno sequence are operably linked to the DNA of the invention, i.e., they are positioned so as to promote transcription of messenger RNA from the DNA.

Eukaryotic microbes such as yeast cultures may also be transformed with vectors of the present invention. *See, e.g.*, U.S. Patent No. 4,745,057. *Saccharomyces cerevisiae* is the most commonly used yeast, although other yeast may also be used. Yeast vectors may contain an origin of replication from the 2 micron yeast plasmid or an autonomously replicating sequence (ARS), a promoter, a JSY3 coding region, sequences for polyadenylation and transcription termination, and a selection gene. An exemplary plasmid is YRp7, (Stinchcomb et al., *Nature* 282:39 (1979); Kingsman et al., *Gene* 7:141 (1979); Tschemper et al., *Gene* 10:157 (1980)). Suitable promoting sequences in yeast vectors include the promoters for metallothionein, 3-phosphoglycerate kinase (Hitzeman et al., J. Biol. Chem. 255:2073 (1980) or other glycolytic enzymes (Hess et al., *J. Adv. Enzyme Reg*. 7:149 (1968); and Holland et al., *Biochemistry* 17:4900 (1978)).

Host cells such as insect cells (e.g., cultured *Spodoptera frugiperda* cells) and expression vectors such as the baculovirus expression vector (e.g., vectors derived from *Autographa californica* MNPV, *Trichoplusia ni* MNPV, *Rachiplusia ou* MNPV, or *Galleria ou* MNPV) may be employed in carrying out the present invention, as described in U.S. Patents Nos. 4,745,051 and 4,879,236 to Smith et al. In general, a baculovirus expression vector comprises a

baculovirus genome containing the gene or coding region to be expressed inserted into the polyhedrin gene at a position ranging from the polyhedrin transcriptional start signal to the ATG start site and under the transcriptional control of a baculovirus polyhedrin promoter.

Examples of useful mammalian host cell lines are VERO and HeLa cells, Chinese hamster ovary (CHO) cell lines, and WI138, BHK, COS-7, CV, and MDCK cell lines. The transcriptional and translational control sequences in expression vectors to be used in transforming vertebrate cells are often provided by viral sources. For example, commonly used promoters are derived from polyoma, Adenovirus 2, and Simian Virus 40 (SV40). *See, e.g.*, U.S. Patent No. 4,599,308. An origin of replication may be provided either by construction of the vector to include an exogenous origin, such as may be derived from SV40 or other viral (e.g. Polyoma, Adenovirus, VSV, or BPV) source, or may be provided by the host cell chromosomal replication mechanism. If the vector is integrated into the host cell chromosome, the latter is often sufficient. Rather than using vectors which contain viral origins of replication, one can transform mammalian cells by the method of cotransformation with a selectable marker and DNA of the present invention, as described in U.S. Pat. No. 4,399,216.

Alternatively, the invention DNA sequences can be translated into RNA, which can then be transfected into amphibian cells for transcription into protein. Suitable amphibian cells include Xenopus oocytes.

Use of the phrase "substantial sequence similarity" in the present specification and claims means that DNA, RNA or amino acid sequences which have slight and non-consequential sequence variations from the actual sequences disclosed and claimed herein are considered to be equivalent to the sequences of the present invention. In this regard, "slight and non-consequential sequence variations" mean that "similar" sequences (i.e., the sequences that have substantial sequence similarity with

the DNA, RNA, or proteins disclosed and claimed herein) will be functionally equivalent to the sequences disclosed and claimed in the present invention. Functionally equivalent sequences will function in substantially the same manner to produce substantially the same compositions as the nucleic acid and amino acid compositions disclosed and claimed herein.

As used herein, the term 'gene' refers to a DNA sequence that incorporates (1) upstream (5') regulatory signals including the promoter, (2) a coding region specifying the product, protein or RNA of the gene, (3) downstream (3') regions including.transcription termination and polyadenylation signals and (4) associated sequences required for efficient and specific expression.

The term 'promoter' refers to a region of a DNA sequence that incorporates the necessary signals for the efficient expression of a coding sequence. THis may include sequences to which an RNA polymerase binds but is not limited to such sequences and may include regions to which other regulatory proteins bind together with regions involved in the control of protein translation and may include coding sequences.

D. Vaccines and Vaccine Formulations.

The present invention provides for a variety of different vaccines useful for protecting feline species against FIV. Examples include live attenuated clone JSY3 virus, fixed whole virus, host cells which express virus antigen on the surface thereof (with the cells optionally fixed), preparations of virus fragments, purified proteins, antigenic fragments of proteins, and antigenic peptides which are derivatives of the antigenic fragments (as discussed in detail below). These various compounds and mixtures are generically referred to herein as active agents.

Live attenuated FIV clone JSY3 virus is made by serial passage of the virus in tissue culture or genetically

altered by recombinant techniques, in accordance with known procedures. Fixed virus is made by contacting live virus (attenuated or unattenuated) to a suitable fixative, such as formalin.

Preparations of viral fragments are made by lysing host cells, such as *E. coli* cells, transformed with a vector encoding the FIV of the present invention or a portion thereof. For example, the vector may encode a JSY3 DNA segment which produces hollow virus particles which are antigenic. The lysate may be used in crude form, partially purified, or a particular viral protein (or antigenic fragment thereof) such as the envelope protein purified to homogeneity, and used as an active agent for a vaccine against FIV.

Host cells such as yeast cells may be transformed with vectors of the present invention capable of expressing JSY3 proteins, or antigenic fragments thereof, on the surface of the host cells, and the transformed host cells used as an active vaccine agent per se or fixed (e.g., with formalin) and used as an active agent.

Antigenic peptides are selected from the group consisting of antigenic fragments of FIV clone JSY3 proteins, such as the envelope protein, the gag open reading frame product, and gag peptides (such as p10, p15, p24a, p25) and the antigenic equivalents thereof (i.e., analogs or derivatives). Antigenic peptides may be chemically synthesized or produced by recombinant techniques. The antigenic fragments are preferably not more than 20 amino acid residues in length, and are more preferably not more than 10 amino acid residues in length. The antigenic equivalents are selected from the group consisting of: (a) modified peptides comprising the aforesaid antigenic fragments modified by the inclusion of one or more changes to the amino acid sequence thereof; and (b) longer peptides which incorporate the sequence of the aforesaid fragments or the aforesaid modified peptides and which have (i) up to four extra amino acid residues

attached to the C-terminal end thereof, (ii) up to four extra amino acid residues attached to the N-terminal end thereof, or (iii) up to four extra amino acid residues attached to the C-terminal end thereof and up to four extra amino acid residues attached to the N-terminal end thereof.

The term "antigenic equivalents," as used herein, refers to proteins or peptides which bind to an antibody which binds to the protein or peptide with which equivalency is sought to be established. Antibodies which are used to select such antigenic equivalents are referred to as "selection antibodies" herein. Preferred selection antibodies are monoclonal antibodies which bind to clone JSY3, but preferably not to isolates of FIV other than FIV strain $NCSU_1$ (such as the Petaluma strain isolated by N. Pedersen), and most preferably not to other molecular clones of FIV $NCSU_1$.

One or more amino acids of an antigenic peptide sequence may be replaced by one or more other amino acids which does not affect the antigenicity of that sequence. Such changes can be guided by known similarities between amino acids in physical features such as charge density, hydrophobicity/hydrophilicity, size and configuration. For example, Thr may be replaced by Ser and vice versa, Asp may be Replaced by Glu and vice versa, and Leu may be replaced by Ile and vice versa.

Antigenic equivalents may be formed by modifying reactive groups within a natural sequence or modifying the N-terminal amino and/or C-terminal carboxyl group. Such equivalents include salts formed with acids and/or bases, particularly physiologically acceptable inorganic and organic acids and bases. Other equivalents include modified carboxyl and/or amino groups on the synthetic peptide to produce esters or amides, or amino acid protecting groups such as N-t-butoxycarbonyl. Preferred modifications are those which provide a more stable, active peptide which will be less prone to enzymatic degradation *in vivo*.

For use as a vaccine, the active agents of the present invention may be administered to the subject by any suitable means. Exemplary are by intramuscular injection, by subcutaneous injection, by intravenous injection, by intraperitoneal injection, by oral injection, and by nasal spray.

The amount of active agent administered will depend upon factors such as route of administration, species, and the use of booster administrations. In general, a dosage of about .1 to about 100 μg per pound subject body weight may be used, more particularly about 1 μg per pound.

Vaccine formulations of the present invention comprise the active agent in a pharmaceutically acceptable carrier. The active agent is included in the carrier in an amount effective to protect the subject being treated. Pharmaceutically acceptable carriers are preferably liquid, particularly aqueous, carriers, such as sodium phosphate buffered saline. The vaccine formulation may be stored in a sterile glass container sealed with a rubber stopper through which liquids may be injected and formulations withdrawn by syringe.

Vaccine formulations of the present invention may optionally contain one or more adjuvants. Any suitable adjuvant can be used, exemplary being aluminum hydroxide, aluminum phosphate, plant and animal oils, synthetic polymers and the like, with the amount of adjuvant depending on the nature of the particular adjuvant employed. In addition, the vaccine formulations may also contain one or more stabilizer, exemplary being carbohydrates such as sorbitol, mannitol, starch, sucrose, dextrin, and glucose, proteins such as albumin or casein, and buffers such as alkaline metal phosphates and the like.

E. Infection of Cats with FIV clone JSY3.

Cats infected with FIV clone JSY3 are useful as a model system for the study of retroviral infections, such as by HIV. Cats used for this purpose are preferably specific

pathogen-free (SPF) cats, which are commercially available from sources such as Charles River Laboratories and Berkshire Laboratories. Infected cats are preferably maintained as a single colony of two or more cats, all infected with FIV clone JSY3. The colony may be maintained in a single room with each cat housed in an appropriate cage, in accordance with standard practices for the maintenance of animals. A colony will consist of a plurality of infected cats, typically from ten, fifteen, twenty, thirty or more cats; the number of individual cats will vary according to need. Preferably, all members of the colony are SPF cats (i.e., free of pathogens other than FIV clone JSY3).

SPF cats may be infected with FIV clone JSY3 by any suitable means, such as by intraperitoneal, intravenous, or subcutaneous injection with a solution containing FIV clone JSY3. The solution may be blood from a previously infected cat, a blood fraction containing peripheral blood mononuclear cells from a previously infected cat, a pharmaceutically acceptable carrier such as saline solution containing FIV clone JSY3, etc.

Cats infected with FIV clone JSY3 are particularly useful as a model system for immunodeficient states associated with retroviral infection because of the rapid inversion of the $CD4^+$:$CD8^+$ ratio caused by JSY3. When used as a model system, the cat or cats infected with FIV clone JSY3 is subjected to a treatment, which treatment is a candidate for use in combating retroviral infections, and the progress of the FIV infection cat or cats thereafter examined. A control group of cats infected with FIV clone JSY3 but untreated, or placebo treated, may be included as a control group. A slowing in the progression of the disease in the cats indicates that the treatment may be useful for combating retroviral diseases in other animal subjects. Typically, the candidate treatment will then be subjected to further screening procedures and toxicological testing to determine whether the treatment may be

clinically useful. The treatment to which the cats are subjected may be any treatment, such as the administration of candidate drugs (e.g., candidate antiretroviral compounds) or drug combinations, including small organic compounds, peptides, or proteins, which may be administered orally or parenterally, or may involve treatments other than the administration of drugs such as a biological response modifier or a vaccine. The progress of the disease in the cats after treatment can be monitored by any suitable means, such as examination for inhibition of the deterioration of $CD4^+$ cell levels, declines in the circulating levels of the FIV GAG protein, the weight of the cat and its general appearance, etc.

An advantage of using JSY3 infected cats as a model for retroviral disease as described above is that the FIV virus is not infectious to humans. A disadvantage of this model is that cats are somewhat large animals; mice are much more practical as animal models of disease.

An additional aspect of the present invention is an immunodeficient mouse containing feline tissue, which feline tissue is capable of infection with feline immunodeficiency virus (FIV). The mouse is infected with FIV clone JSY3, and used as an animal model in essentially the same manner as cats as described above. Any suitable immunodeficient mouse may be employed, such as SCID mice (e.g., the C.B.-17 *scid/scid* mouse) athymic mice such as the nude mouse, and mice which have been rendered immunodeficient by treatment with radiation. The mouse may be deficient in T lymphocytes function alone (e.g., athymic mice), but is preferably deficient in both T and B lymphocyte function.

The feline tissue which the immunodeficient mice contains preferably comprises one or more of the following: feline thymus tissue, feline lymph node tissue, feline liver cells, feline bone marrow cells, feline peripheral blood mononuclear cells such as peripheral blood lymphocytes and peripheral blood monocytes, and feline

spleen cells. The feline tissue may be introduced into the mouse by any suitable means, such as intraperitoneal injection, intravenous injection, surgical implantation, and combinations thereof. Feline tissue may be introduced as organized tissues (e.g., thymus and lymph node) or as discrete cells. One example is an immunodeficient mouse having feline thymus tissue and/or lymph node tissue surgically implanted. Another example is an immunodeficient mouse into which peripheral blood mononuclear cells have been intraperitoneally injected.

F. Diagnostic Probes.

The FIV clone JSY3 nucleotide sequence can be used to generate hybridization probes which specifically bind to FIV clone JSY3 genetic material, or the genetic material of FIV clones having all of, or essentially all of, the identifying characteristics of FIV clone JSY3, to determine the presence of such FIV in cats. The hybridization probe may be selected so that it does not bind to known FIV isolates (such as the Petaluma strain) other than $NCSU_1$, or to any FIV isolate or clone other than JSY3. Hybridization probes may be cDNA fragments or oligonucleotides, and may be labelled with a detectable group as discussed hereinbelow. Pairs of probes which will serve as PCR primers for the JSY3 genome or a portion thereof may be used in accordance with the process described in U.S. Patents Nos. 4,683,202 and 4,683,195.

For example, an illustrative embodiment of the above probes comprises DNA sequences set forth in SEQ ID NOS:4, 5, 7, 9, 11, 13, 14, 16, 18, and 19, or suitable fragments thereof.

The term "labelled" is used herein to refer to the conjugating or covalent bonding of any suitable detectable group, including enzymes (e.g., horseradish peroxidase, β-glucuronidase, alkaline phosphatase, and β-D-galactosidase), fluorescent labels (e.g., fluorescein, luciferase), and radiolabels (e.g., ^{14}C, ^{131}I, ^{3}H, ^{32}P, and

^{35}S) to the compound being labelled. Techniques for labelling various compounds, including proteins, peptides, and antibodies, are well known. *See, e.g.*, Morrison, *Methods in Enzymology* **32b**, 103 (1974); Syvanen et al., *J. Biol. Chem.* **284**, 3762 (1973); Bolton and Hunter, *Biochem. J.* **133**, 529 (1973).

G. DNA Sequence and Genome Organization

Isolated DNA from the JSY3 provirus may be used to generate hybridization probes, which may be used in diagnostic assays as discussed above. Isolated DNA capable of expressing antigenic proteins or antigenic fragments thereof may be used for producing proteins which are also useful in diagnostic assays.

An aspect of the present invention is oligonucleotide probes which selectively hybridize to DNA encoding a group antigen (gag) polypeptide (or an antigenic fragment thereof) of FIV clone JSY3 under stringent conditions, which probes do not bind to DNA encoding the group antigen (gag) polypeptide of the following known FIV strains under the same stringency conditions: FIV-Petaluma (U.S. Patent No. 5,037,753); FIV-PPR (Phillips *et al.*, *J. Virology*, 64:4605 (1990)); FIV-TM1 and FIV-TM2 (Miyazawa *et al.*, *Arch. Virology* 108:59 (1989)); FIV-UT113 (Verschoor *et al.*, *J. Cell. Biochem.*, Suppl. 14D:143 (1990). Conditions which will permit other DNA coding for an FIV gag polypeptide to hybridize to the DNA of FIV clone JSY3 gag polypeptide can be determined in a routine manner. For example, hybridization may be carried out under conditions of reduced stringency or even stringent conditions (e.g., conditions represented by a wash stringency of 0.3M NaCl, 0.03M sodium citrate, and 0.1% SDS at 60°C or even 70° C) to DNA encoding the gag polypeptide of FIV clone JSY3 disclosed herein in a standard *in situ* hybridization assay. *See* J. Sambrook et al., Molecular Cloning, A Laboratory Manual (2nd Ed. 1989)(Cold Spring Harbor Laboratory)).

In general, DNA which codes for FIV gag polypeptide or

antigenic fragments thereof and which hybridizes to DNA encoding gag polypeptide (or antigenic fragments thereof) of FIV clone JSY3 disclosed herein will have at least 75%, 80%, 85%, or even 90% or more sequence similarity with the DNA of the gag polypeptide (or antigenic fragments thereof) of FIV clone JSY3 disclosed herein. Further, DNA which codes for FIV gag polypeptide (or antigenic fragments thereof), or which codes for a gag polypeptide or antigenic fragment coded for by DNA which hybridizes to the DNA which codes for FIV clone JSY3 gag polypeptide or antigenic fragment thereof, but which differ in codon sequence from these due to the degeneracy of the genetic code, are also an aspect of this invention. The degeneracy of the genetic code, which allows different nucleic acid sequences to code for the same protein or peptide, is well known in the literature. *See, e.g.*, U.S. Patent No. 4,757,006 to Toole et al. at Col. 2, Table 1.

A particular embodiment of the foregoing also disclosed herein is isolated DNA encoding the group antigen (gag) polypeptide or an antigenic fragment thereof, of FIV clone JSY3, and isolated DNA encoding the envelope protein or an antigenic fragment thereof, where the DNA is: **(a)** isolated DNA encoding group antigen (gag) polypeptide or envelope protein, or an antigenic fragment thereof, of FIV clone JSY3, **(b)** isolated DNA which hybridizes to isolated DNA of (a) above under stringent conditions and which encodes a feline immunodeficiency virus group antigen (gag) polypeptide, envelope protein, or antigenic fragment thereof with at least 75%, 80%, 85% or even 90% or more sequence similarity to isolated DNA of (a) above; or **(c)** isolated DNA differing from the isolated DNAs of (a) and (b) above in nucleotide sequence due to the degeneracy of the genetic code, and which encodes a feline immunodeficiency virus group antigen (gag) polypeptide, envelope protein, or antigenic fragment thereof encoded by the isolated DNAs of (a) or (b), above.

An illustrative embodiment of the foregoing DNA which

codes for FIV clone JSY3 gag polypeptide (or antigenic fragments thereof) is DNA according to SEQ ID NO:4 or a portion thereof; DNA according to SEQ ID NO:5 (p15) or a portion thereof; DNA according to SEQ ID NO:7 (p25) or a portion thereof; DNA according to SEQ ID NO:9 (p24a) or a portion thereof; DNA according to SEQ ID NO:11 (p10) or a portion thereof. An illustrative embodiment of the foregoing DNA which codes for FIV clone JSY3 envelope protein (or antigenic fragments thereof) is SEQ ID NO:18 or SEQ ID NO:19. Also disclosed herein are recombinant DNA sequences comprising vector DNA and a DNA encoding group specific antigen (gag) polypeptides of clone JSY3, or the envelope protein of JSY3, or antigenic fragments thereof (as given above).

The FIV provirus includes the structural genes for group-specific antigens (gag gene), envelope proteins (env gene) and reverse transcriptase (pol gene), as well as several short open reading frames similar to those of other lentiviruses. Omsted *et al.*, *Proc. Natl. Acad. Sci. USA*, **86**, 2448 (1989); Olmsted *et al.*, *Proc. Natl. Acad. Sci. USA*, **86**, 8088 (1989). The gag gene of FIV has been reported to encode a polyprotein of about 450 amino acids, which is subjected to postranslational cleavage. Talbot *et al.*, *Proc. Natl. Acad. Sci. USA*, 86, 5743 (1989); Phillips *et al.*, *J. Virology*, **64**, 4605 (1990). The gag gene and its predicted protein product has been reported to be highly conserved among isolates of FIV. Phillips *et al.*, *J. Virology*, **64**, 4605 (1990); Morikawa *et al.*, *Virology*, **183**, 288 (1991). FIV gag gene has been expressed in baculovirus vectors and assembled into virus-like particles. Morikawa *et al.*, *Virology*, **183**, 288 (1991).

Isolated and purified FIV clone JSY3 group antigen (gag) polypeptide, envelope protein, or antigenic fragments thereof are also an aspect of the present invention. These polypeptides or fragments are coded for by: **(a)** isolated DNA which encodes group antigen (gag) polypeptide or envelope protein, or an antigenic fragment thereof, of FIV

clone JSY3; **(b)** isolated DNA which hybridizes to isolated DNA of (a) above under stringent conditions and which encodes a FIV gag polypeptide, envelope protein, or antigenic fragment thereof with at least 75% sequence similarity to isolated DNA of (a) above; or **(c)** isolated DNA differing from the isolated DNAs of (a) and (b) above in nucleotide sequence due to the degeneracy of the genetic code, and which encodes a FIV gag polypeptide, envelope protein, or antigenic fragment thereof encoded by DNAs of (a) or (b), above. By antigenic polypeptide is meant a polypeptide which is able to raise (with the aid of an adjuvant if necessary) an antibody response in cats. The polypeptide may be a fragment of a polypeptide naturally occurring in FIV particles. The fragment may be from a naturally occurring polypeptide or produced by isolation or synthesis of a gene or coding region encoding a desired polypeptide and expression within an appropriate expression system.

An illustrative embodiment of the foregoing polypeptides is the JSY3 group antigen specific polypeptide (SEQ ID NO:2) and peptides thereof (SEQ ID NO:6 (p15); SEQ ID NO:8 (p25); SEQ ID NO:10 (p24a); SEQ ID NO:12 (p10)); and the JSY3 envelope protein (SEQ ID NO:3) and TM protein (SEQ ID NO:19).

The present invention is explained in greater detail in the non-limiting Examples set forth below.

EXAMPLE 1

Materials and Methods

Viruses. The biological parent virus isolate FIV-NCSU$_1$ (US Patent No. 5,413,927 to Tompkins et al.) was obtained from the peripheral blood mononuclear cells (PBMCs) of a cat naturally infected with FIV and has been described elsewhere (Davidson et al., *Am. J. Pathol*. 143:1486 (1993); English et al., *J. Virol*. 67:5175 (1993); English et al., *J. Infect. Dis*. 170:543 (1994); Tompkins et al., *J. Am. Vet. Med. Assoc*. 199:1311 (1991)). The NCSU$_1$ isolate (or

"NCSU-1") is available from the American Type Culture Collection (ATCC Number VR2333), 12301 Parklawn Drive, Rockville, Maryland 20852 USA (deposited in accordance with the provisions of the Budapest Treaty, July 23, 1991). See U.S. Patent 5,413,927 to Tompkins et al. The FIV-NCSU$_1$ molecular clone JSY3 inoculum was collected from an FCD4E feline lymphocyte culture which had been cocultured with transfected Crandell feline kidney (CrFK) cells (see below).

Molecular cloning of the FIV proviral genome. Genomic DNA was isolated by equilibrium centrifugation in CsCl-ethidium bromide gradients (Maniatis et al., *Molecular cloning: A laboratory manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY) from 5 x 10^7 FCD4E cells (interleukin-2-dependent, FIV-NCSU$_1$-infected feline CD4+ lymphocytes) inoculated with FIV-NCSU$_1$ obtained from the original source cat. As shown in **Figure 4**, FCD4E genomic DNA which had been partially digested with *Sau*3AI and size fractionated was cloned into the EMBL3 lambda vector arm. Genomic libraries were screened primarily by plaque hybridization with a *gag* region PCR product probe (838 bp) as described elsewhere (Maniatis et al., *Molecular cloning: A laboratory manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY). A full-length clone was identified by PCR of phage suspension with six primer sets designed from FIV-14 sequences (GenBank accession no. M25381). These primer sets amplified 5′ long terminal repeat, *gag*, *env*, and 3′ long terminal repeat regions under the PCR conditions described below. The following primers were used for identification of the full-length lambda clone JSY3 (each primer designated by the 5′ nucleotide of the complete FIV-14 sequence): 3U (U3) 5′-GGA TGA GTA TTG GAA CCC TGA A-3′ (SEQ ID NO:21); 337L (U5) 5′-GAT TCC GAG ACC TCA CAG GTA A-3′ (SEQ ID NO:22); 447U 5′-AAT AGG GAA GCA GTA GCA GAC-3′ (SEQ ID NO:23); 829L 5′-GTA AAT CGC AAA TAA CCA ACC-3′ (SEQ ID NO:24); 919U (FIV7) 5′-TGA CGG TGT CTA CTG CTG CT-3′ (SEQ ID NO:25); 1756L (FIV8) 5′-CAC ACT GGT

CCT GAT CCT TTT-3′ (SEQ ID NO:26); 1057U 5′-CCA CAA TAT GTA GCA CTT GAC C-3′ (SEQ ID NO:27); 1639L 5′-GGG TAC TTT CTG GCT TAA GGT G-3′ (SEQ ID NO:28); 6938U 5′-GGG GGA CCT ACC TTG GGG AAT TGG GCT-3′ (SEQ ID NO:29); 7252L 5′-GGT GAT CAT GAT CAG TGG GAT TTG TAA TGG GTC TG-3′ (SEQ ID NO:30); 7252L 5′-GGT GAT CAT GAT CAG TGG GAT TTG TAA TGG GTC TG-3′ (SEQ ID NO:31); 8859U 5′-ATA AGG GAG ATA CTG TGC TGA-3′ (SEQ ID NO:32); 9029L 5′- GCG ATC TTC TAA CTC TGT CAT-3′ (SEQ ID NO:33).

DNA transfection. Ten micrograms of lambda clone DNA was transfected into CrFK and AH927 (a feline embryonic fibroblast cell line) cells by using the cationic liposome DOTAP (Boehringer Mannheim, Indianapolis, Ind.) according to the manufacturer's protocol. Twenty-four hours after transfection, these cells were cocultured for 72 hours with FCD4E or concanavalin A (10 μg/ml)-stimulated normal cat PBMCs. FCD4E (or PBMCs) and CrFK (or AH927) cells were then cultured separately. Culture supernatant was collected at 3- to 4- day intervals and assayed for RT activity. Pooled samples for *in vivo* infection were titrated in FCD4E cells by the 50% tissue culture infective dose ($TCID_{50}$) method.

***In vitro* infections with JSY3 clone.** Cultures of FCD4E or DEAE-dextran-treated CrFK cells were inoculated with cell-free FIV-$NCSU_1$ JSY3 clone containing 2 x 10^4 cpm of RT activity. The culture supernatant was collected twice weekly and assayed for RT activity.

***In vivo* FIV infection.** Six 6-month old female cats were inoculated intravenously with 10^6 $TCID_{50}$s of the JSY3 clone. Nine age- and sex-matched specific-pathogen-fee (SPF) cats were inoculated with wild-type FIV-$NCSU_1$, and nine mock-infected SPF cats were used as controls. The wild-type FIV-$NCSU_1$ infected group was examined up to 18 weeks post infection (p.i.) in parallel with the JSY3-infected cats.

Blood sampling. Whole blood was collected by jugular venipuncture into sodium citrate anticoagulant tubes. Aliquots were removed for complete blood counts and flow

cytometry, and plasma was collected for anti-FIV antibody assays. PBMCs were purified over Percoll as described (Tompkins et al., *Vet. Immunol. Immunopathol.*, 16:1 (1987)). PBMCs were then cocultured with FCD4E cells for infectious virus recovery, lysed for provirus detection by PCR, or sorted for lymphocyte subset tropism studies.

Lymphocyte subset analysis by flow cytometry. Lymphocyte subsets were determined by two-color flow cytometric analysis as described (Davidson et al., *Am. J. Pathol.* 143:1486 (1993)) using a panel of monoclonal antibodies (MAbs) (Tompkins et al., *Vet. immunol. Immunopathol.* 26:305 (1990)). Briefly, plasma was removed, the cells were washed twice in phosphate-buffered saline (PBS), and MAbs were added in a combination of fluorescein isothiocyanate-labeled anti-cat immunoglobulin (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, MD) and biotin-labeled anti-pan T-cell antibodies or fluorescein isothiocyanate-labeled anti-CD8 and biotin-labeled anti-CD4 antibodies. Biotin-labeled antibodies were developed with phycoerythrin. Erythrocytes were lysed with fluorescence-activated cell sorter (FACS) lysing solution (Becton Dickinson Immunocytometry Systems, San Jose, CA), and the percent positively stained lymphocytes was determined by flow cytometric analysis using a Becton Dickinson FACScan. The absolute numbers for each lymphocyte subset were calculated by multiplying the percent positive cells by the total number of lymphocytes, determined by a complete blood count and differential performed on the blood sample.

PCR-Southern blot analysis for FIV-provirus detection. Percoll-purified PBMCs were washed with PBS, and cell pellets were stored at -70°C until assayed. Cells (10^6) were lysed in 200 μl of 1 x PCR buffer and digested with 600 μg of proteinase K per ml. An 838-bp length of the FIV *gag* region was amplified with the primer set 919U-1756L. Amplification was performed as described previously (English et al., *J. Virol.* 67:5175 (1993)), with minor modifications. Briefly, 2 μl of cell lysate (equivalent to

10^4 cells) was amplified in a 100-μl PCR mixture (1 x PCR buffer, 1.5 mM $MgCl_2$, 200 μM each deoxynucleoside triphosphate, 0.5 μM each primer, and 2.5 U of *Taq* DNA polymerase over 40 cycles (one cycle was 94°C for 1 minute, 59°C for 2 minutes, and 72°C for 1 minute, final extension was done at 72°C for 10 minutes). Amplified products were resolved on a 1.2% agarose gel, blotted, and hybridized with radiolabeled internal oligonucleotides probe.

Western blot analysis for plasma antibody to FIV. The Western blot (immunoblot) assay was performed as described (Novotney et al., *AIDS* 4:1213 (1990)).

RT activity assay. The Mg^{2+} -dependent RT activity assay was performed as described (Novotney et al., *AIDS* 4:1213 (1990)) and is a modification of a procedure of Goff et al. (Goff et al., *J. Virol.* 38:239 (1981)).

Lymphocyte subset sorting of feline PBMCs. The JSY3 clone-infected cat PBMCs were sorted into CD4+, CD8+ and B lymphocyte subsets using MiniMACS (Miltenyi Biotec, Sunnyvale, CA) magnetic beads. Percoll-enriched PBMCs were divided among three tubes and incubated at 4°C for 30 minutes with biotin-labeled anti-CD4 or anti-CD8 or anti-canine B-cell MAb (B5) for a non-immunoglobulin-positive B-cell epitope (English et al., *J. Virol.* 67:5175 (1993)). Streptavidin-conjugated MiniMACS beads were then added, and the cells were incubated for an additional 20 minutes at 4°C and then positively sorted. A fraction of each sorted subset was analyzed for purity by two-color flow cytometry. Cells were stained with biotin-labeled MAbs, developed with phycoerythrin-conjugated streptavidin, and analyzed on the FACScan. The remaining sorted lymphocytes were stored at -70°C until they were assayed for the presence of FIV provirus by PCR-Southern blotting.

***T. gondii* infection.** Twenty-nine weeks after infection with the JSY3 clone, cats were inoculated via the carotid artery with 10,000 tachyzoites of the ME49 strain of *T. gondii* as described (Davidson et al., *Am. J. Pathol.* 143:1486 (1993)). Six age- and sex-matched SPF cats were

also inoculated with *T. gondii* as controls. The cats were examined daily for clinical signs of illness using scoring criteria (Davidson et al., *Am. J. Pathol.* 143:1486 (1993)). Cats with severe clinical signs indicative of generalized toxoplasmosis were euthanized by barbiturate overdose.

Postmortem examination. Following euthanasia, a gross necropsy was performed and tissues were sampled for microscopic examination. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin stain.

EXAMPLE 2

Molecular Cloning and Sequencing of the JSY3 Proviral Genome

A total of 5×10^7 FCD4E cells were infected with wild-type FIV-NCSU$_1$ from the FIV-NCSU$_1$ source cat. Genomic DNA from this culture was cloned into the EMBL3 lambda vector arm. Primary hybridization-positive clones, determined by plaque hybridization with a randomly labeled 838 bp FIV *gag* PCR product probe, were screened further by PCR as described in Example 1. Five microliters of phage plaque suspensions of each hybridization-positive clone was directly amplified with six different primer sets, and a full-length proviral clone was identified (designated JSY3). The specificity of each FIV PCR product was established by comparing it with the FIV-pPPR plasmid clone (Phillips et al., *J. Virol.* 64:4605 (1990)).

The genomic proviral insert was subcloned into pJEM vectors, and the provirus genome was sequenced by primer directed sequencing, using techniques as are known in the art. Nucleotide and predicted amino acid sequences were computer analyzed, and open reading frames (orfs) were identified.

The provirus DNA sequence of the JSY3 provirus clone of FIV-NCSU$_1$ is provided in **Figure 1**, with the group specific antigen (*gag*), polymerase (*pol*), and envelope protein (*env*) regions marked. As shown in **Figure 1**, the DNA sequence

consists of 9471 base pairs (SEQ ID NO:1).

The coding region of *gag* is nucleotides 631-1980 of SEQ ID NO:1 (SEQ ID NO:4) and encodes a 450 amino acid product (SEQ ID NO:2).

The coding region for the p15 protein is nucleotides 631-1035 of SEQ ID NO:1 (SEQ ID NO:5), with a polypeptide product of 135 amino acids (SEQ ID NO:6).

The coding region for the p25 protein is nucleotides 1036-1704 of SEQ ID NO:1 (SEQ ID NO:7), with a polypeptide product of 223 amino acids (SEQ ID NO:8).

The coding region for the p24a protein is nucleotides 1264-1305 of SEQ ID NO:1 (SEQ ID NO:9), with a polypeptide product of 14 amino acids (SEQ ID NO:10).

The coding region for the p10 protein is nucleotides 1717-1980 of SEQ ID NO:1 (SEQ ID NO:11), with a polypeptide product of 88 amino acids (SEQ ID NO:12).

The coding region of *pol* is amino acids 2151-5991 of SEQ ID NO:1 (SEQ ID NO:13). Two open reading frames (orfs) are found in the *pol* region. Orf 1 is nucleotides 2151-5243 of SEQ ID NO:1 (SEQ ID NO:14), encoding a product of 1031 amino acids (SEQ ID NO:15); Orf 2 is nucleotides 5239-5991 of SEQ ID NO:1 (SEQ ID NO:16) and encodes a product of 251 amino acids (SEQ ID NO:17).

The *env* coding region is nucleotides 6269-8824 of SEQ ID NO:1 (SEQ ID NO:18) and encodes a protein of 852 amino acids (SEQ ID NO:3). The transmembrane (TM) peptide is encoded by nucleotides 8339-8374 of SEQ ID NO:1 (SEQ ID NO:19), and is 12 amino acids in length (SEQ ID NO:20).

Figure 2 aligns the *gag* open reading frames of the JSY3 clone of $NCSU_1$ (FIV-NCSU) with known FIV isolates FIV PPR, FIV Z1, FIV CG, FIV 14, FIV TM1, and FIV TM2. **Figure 3** aligns the whole envelope protein sequence of clone JSY3 of $NCSU_1$ with known FIV isolates FIV 14, FIV Z1, FIV CG, FIV 19k, and FIV PPR.

EXAMPLE 3

Biological Activity of JSY3

To determine the biological activity of the JSY3 clone, lambda DNA was transfected into CrFK, AH927, and FCD4E cells, which were then cocultured with FCD4E cells or PBMCs. While no RT activity was detected in culture supernatants of JSY3-transfected CrFK or AH927 cells when cultured alone, RT activity was detected when the transfected cells were cocultured with either PBMCs or FCD4E cells (data not shown). The replication kinetics of FIV in FCD4E cells is more rapid than in PBMCs because of the greater percentage of CD4+ cells in the FCD4E culture. Supernatants collected at 15 and 19 days of culture from FCD4E cells were filtered (0.2 μm pore size) and stored in aliquots for use an *in vitro* and *in vivo* inocula. These inocula were designated the FIV-NCSU$_1$-JSY3 clone. No RT activity was detected in the FCD4E cultures directly transfected with JSY3, suggesting that the transfection was unsuccessful (data not shown).

To determine the *in vitro* infectivity of the JSY3 clone, FCD4E and CrFK cells were inoculated with cell-free JSY3 clone. Similarly to the FIV-NCSU$_1$ wild-type virus (English et al., *J. Virol.* 67:5175 (1993)), the JSY3 clone replicated efficiently in FCD4E cells, resulting in syncytium formation and cell death (data not shown). However, the JSY3 clone was unable to infect CrFK cells.

EXAMPLE 4

In vivo Infectivity of JSY3

To determine the *in vivo* infectivity of the JSY3 molecular clone, six SPF cats were inoculated intravenously with 10_6 TCID$_{50}$ of JSY3 clone. Nine age-matched SPF cats were inoculated with 10^6 TCID$_{50}$s of FIV-NCSU$_1$, also produced in FCD4E cells. Plasma and PBMCs were collected at various times post infection, and tested for antibodies to FIV by Western blotting and tested for cell-associated FIV

provirus by PCR. As previously reported (English et al., *J. Infect. Dis.* 170:543 (1994); Tompkins et al., *J. Am. Vet. Med. Assoc.* 199:1311 (1991)) cats infected with FIV-$NCSU_1$ parent virus were anti-FIV positive by 4 weeks post infection and were provirus positive by PCR by 2 weeks post infection (data not shown).

The response of cats infected with the JSY3 clone was similar to that of the cats infected with the wild-type. By four weeks post infection, all six cats had antibody to the FIV *gag* proteins p17 and p24, and they were still antibody positive at 25 weeks post infection (data not shown). The presence of FIV provirus in PBMCs from six cats infected with the JSY3 clone was determined by PCR and southern analysis. A PBMC lysate (equivalent to 10^4 cells) was amplified with the *gag* region primer set 919U-1756L, resolved on an agarose gel, and subjected to Southern blot analysis with a 5'-end-labeled internal probe. Provirus was detected in PBMCs from all cats by two weeks post infection (data not shown). All cats remained provirus positive when the amount of cell lysate in the PCR mixture was increased (data not shown).

To establish the presence of infectious virus in PBMCs from the JSY3-infected cats, PBMCs collected at 6 and 25 weeks post infection were cocultured with FCD4E cells and the supernatants were assayed for RT activity. Syncytium formation and cell death were observed in cocultures from all six cats at both six and 25 weeks p.i. RT activity was detectable in all cocultures by 8 to 10 days and peaked by 16 to 18 days of culture (data not shown).

EXAMPLE 5

Lymphocyte Subset Changes in JSY3-infected Cats

Lymphocyte profiles in naturally and experimentally FIV-infected cats are well documented (Ackley et al., *J. Virol.* 64:5652 (1990); English et al., *J. Infect. Dis.* 170:543 (1994); Hoffmann-Fezer et al., *J. Virol.* 66:1484 (1992); Novotney et al., *AIDS* 4:1213 (1990); Tompkins et

al., *J. Am. Vet. Med. Assoc.* 199:1311 (1991)). To determine whether the JSY3 clone causes hematologic and immunologic abnormalities similar to those of the biological parent FIV-$NCSU_1$, lymphocyte subset profiles were analyzed by two-color flow cytometry. As reported for $NCSU_1$ (English et al., *J. Infect. Dis.* 170:543 (1994); Tompkins et al., *J. Am. Vet. Med. Assoc.* 199:1311 (1991)), both the biological virus and the JSY3 clone caused a panlymphopenia two to four weeks p.i. The parent FIV-$NCSU_1$ and the JSY3 molecular clone caused parallel alterations in the CD4+/CD8+ ratio (data not shown). At six weeks p.i., the mean CD4+/CD8+ cell ratios ($\pm$ standard errors) decreased from 3.48 $\pm$ 0.50 to 1.30$\pm$ 0.21 for the parent virus-infected cats. By using total cell counts and flow cytometric analysis of lymphocyte subsets, the decrease in the CD4+/CD8+ ratio was determined to be the result of a decrease in CD4+ lymphocytes and an increase in CD8+ lymphocytes (data not shown). These results indicate that the JSY3 clone-infected cats have hematologic and immunologic abnormalities, including CD4+ and CD8+ lymphocyte changes similar to those of cats infected with the biological parent virus.

EXAMPLE 6

In vivo Lymphocyte Tropism

The *in vivo* hematopoietic target cells of FIV isolates, including $NCSU_1$, have been reported to be CD4+, CD8+, monocytes, and B lymphocytes (Beebe et al., *J. Virol.* 68:3080 (1994); Brown et al., *J. Virol.* 65:3359 (1991); English et al., *J. Virol.* 67:5175 (1993)). To determine whether the JSY3 molecular clone has a similar panlymphotropism *in vivo*, PBMCs from JSY3 clone infected cats were sorted into CD4+, CD8+, and B lymphocyte populations using antibody-coated magnetic beads. Each cell subset was lysed, PCR amplified with the *gag* region 919U-1756L primer set, and analyzed by Southern blotting. As previously reported for the $NCSU_1$ parent virus, FIV

provirus was first detected in CD4+ lymphoctyes during the acute-stage infection with JSY3 (2 to 4 weeks p.i.)(data not shown). At a later stage of infection (as early as 14 weeks p.i.), FIV provirus was found in CD8+ and B lymphocytes in addition to CD4+ lymphocytes, as reported for FIV-NCSU$_1$ (English et al., *J. Virol.* 67:5175 (1993)). All six JSY3-infected cats showed similar shifts in provirus burden from predominately CD4+ cells during the acute-stage infection to predominately B cells during the asymptomatic stage. While CD4+ and CD8+ cells were not always positive for provirus under PCR conditions described in Example 1, provirus was always able to be detected in these cells during the asymptomatic-stage infection by increasing cell numbers or using nested primers as described by English et al., *J. Virol.* 67:5175 (1993). The JSY3 molecular clone, similar to the parent biological isolate, exhibits a CD4+ tropism during the acute-stage infection that then shifts to a panlymphotropism as the infection progresses.

EXAMPLE 7

JSY3-Infected Cats

Acute-stage disease. In the primary phase of infection (2 to 16 weeks p.i.), both the JSY3- and the parent isolate-infected cats developed low-grade fevers, panlymphopenia, neutropenia, and generalized lymphadenopathy (data not shown), as has been reported for a number of biological isolates of FIV (Yamamoto et al., *Am. J. Vet. Res.* 49:1246 (1988)), including NCSU$_1$ (English et al., *J. Infect. Dis.* 170:543 (1994)).

Clinical response of JSY3-infected cats to *T. gondii* challenge. Davidson et al., (*Am. J. Pathol.* 143:1486 (1993)) reported that FIV-NCSU$_1$ causes immune system impairment in cats as early as eighteen weeks after infection and enhances susceptibility to a primary *t. gondii* infection. To determine if the molecular clone JSY3 caused immune impairment early in the asymptomatic stage of

infection, the cats were parenterally inoculated with the ME49 strain of *T. gondii* 29 weeks after JSY3 infection. six age-matched SPF control cats were similarly infected with *T. gondii*. At the time of *T. gondii* inoculation, all six FIV-infected cats were clinically normal; however, they had a marked decrease in their CD4+/CD8+ ratios in comparison with preinfection ratios and those of the control cats (data not shown). Only one of six *T. gondii*-infected cats in the non-FIV-inoculated group had positive clinical scores, as a result of anorexia and lethargy on days 8 to 11 after inoculation. Cats in this group also developed multifocal chorioretinitis beginning on days 7 to 10 after inoculation, which resolved over a three week course. The infection was otherwise subclinical in these cats. This clinical response is similar to that previously reported for healthy cats challenged with the mildly virulent ME49 strain of *T. gondii* (Davidson et al., *Invest. Ophthalmol. Visual Sci.* 34:3653 (1993); Davidson et al., *Am. J. Pathol.* 143:1486 (1993)).

Five of the six FIV-positive cats challenged with *t. gondii* had positive clinical scores in all three categories (attitude, appetite, and respiratory signs), and the total scores were higher than those of the *T. gondii* control group. Beginning on days 6 to 9 after inoculation, three FIV-infected cats challenged with *T. gondii* developed high fevers, depression, and moderate to severe ocular lesions, including chorioretinitis with subretinal granuloma formation, localized retinal detachment, and fibrinous anterior uveitis. Severe and progressive tachypnea, dyspnea, tachycardia, and icterus were noted, and interstitial and consolidated lung sounds were auscultated. These three cats were euthanized when moribund on day 9 or 10 after inoculation. Two of the three remaining cats developed mild to moderate clinical toxoplasmosis but recovered. This clinical course of *T. gondii* infection in JSY3 infected cats, including the high morbidity, was similar to that reported by Davidson et al. (*Am. J. Pathol.*

143:1486 (1993)) for cats infected with $NCSU_1$.

Postmortem findings. Postmortem exams were performed on the three FIV-*T.gondii*-infected cats that were euthanized to confirm that their clinical disease was due to toxoplasmosis. One cat had gross evidence of interstitial pneumonia. All three animals had foci of discoloration in the liver consistent with hepatic necrosis, and the hearts contained foci of myocardial necrosis. Histologically, lesions were present in the lungs, livers, hearts, and brains of the three cats, and were similar to those seen in cats with dual FIV-$NCSU_1$-*T. gondii* infection as described by Davidson et al., (*Am. J. Pathol.* 143:1486 (1993)). Except for the heart, *T. gondii* tachyzooites were seen in all tissues examined. The tachyzooites were never numerous but most conspicuous as clusters inside of macrophages in the regions of severe inflammation and necrosis in the brain, lung, and liver.

The foregoing examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Tompkins, Wayne A.F.
Tompkins, Mary B.
Yang, Joo-Sung

(ii) TITLE OF INVENTION: Feline Immunodeficiency Virus Clone

(iii) NUMBER OF SEQUENCES: 33

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
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(B) REGISTRATION NUMBER: 37,092
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(B) TELEFAX: 919-881-3175

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9471 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 631..1980

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 6269..8824

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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TCGAGTTCTC CCTTGAGGCT CCCACAGATA CAATAAATAT TTGAGATTGA ACCCTGTCAA     300

GTATCTGTGT AATCTTTTTT ACCTGTGAGG TCTCGGAATC CGGGCCGAGA ACTTCGCAGT     360

TGGCGCCCGA ACAGGGACTT GATTGAGAGT GATTGAGGAA GTGAAGCTAG AGCAATAGAA     420

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AGAGATTTCA CATGGATGGG GACCTGGAAT GGTGGGAATT GTGATAAAAG CTTTTAGTTG 5720

TGGAGAAAGA AAGATTGAGG CTACTCCTGT AATGATTATA AGAGGAGAAA TAGATCCAAA 5780

AAAATGGTGT GGAGATTGTT GGAATTTGAT GTGTCTTAGG AACTCACCTC CACAGACTTT 5840

ACAAAGACTT GCTATGTTGG CATGTGGCGT GCCGGCTAAG GAGTGGCGAG GATGCTGTAA 5900

TCAACGCTTT GTTTCTCCTT ACAGAACGCC TGCTGATTTG GAGGTCATTC AATCCAAGCC 5960

CAGCTGGAGT CTATTATGGT CAGGGAGCCT ATGAATGGAA GACATACTAA CATTATTTAA 6020

TAAGGTCACT AAGAAACTAG AAAAGGAAAA AGCTATCAGA ATATTTGTAT TAGCACATCA 6080

ATTAGAAAGG GACAAAGTTA TTAGATTACT ACAAGGATTA GTTTGGAGAC ATAGATTTAA 6140

GAAACCCCAA ACAAAATACT GTTTATGTTG GTTCTGTTGC AAATTCTACT ATTGGCAGTT 6200

GCAATCTACA TTATCAATAA CTACTGCTTA GAAATACTTA TAATAATATT TCATTTGCAA 6260

CAATAATT ATG GCA GAA GGA TTT GCA GCC AAT AGA CAA TGG ATA GGA CCA 6310
Met Ala Glu Gly Phe Ala Ala Asn Arg Gln Trp Ile Gly Pro
1 5 10

GAA GAA GCT GAA GAG TTA TTA GAT TTT GAT ATA GCA ACA CAA ATG AAT 6358
Glu Glu Ala Glu Glu Leu Leu Asp Phe Asp Ile Ala Thr Gln Met Asn
15 20 25 30

GAA GAA GGG CCA CTA AAT CCA GGG ATG AAC CCA TTT AGG GTA CCT GGA 6406
Glu Glu Gly Pro Leu Asn Pro Gly Met Asn Pro Phe Arg Val Pro Gly
35 40 45

ATA ACA GAT AAA GAA AAG CAA GAC TAT TGT AAC ATA TTA CAA CCT AAG 6454
Ile Thr Asp Lys Glu Lys Gln Asp Tyr Cys Asn Ile Leu Gln Pro Lys
50 55 60

TTA CAA GAT TTA CGG AAT GAA CTT CAA GAG GTA AAA CTA GAA GAA GGA 6502
Leu Gln Asp Leu Arg Asn Glu Leu Gln Glu Val Lys Leu Glu Glu Gly
65 70 75

AAT GCA GGT AAG TTT AGA AGG GCA AGA TAT TTA AGA TAT TCT GAT GAA 6550
Asn Ala Gly Lys Phe Arg Arg Ala Arg Tyr Leu Arg Tyr Ser Asp Glu
80 85 90

AAT GTG CTA TCT ATA GTC TAT TTG CTA ATA GGA TAT CTA AGA TAT TTA 6598
Asn Val Leu Ser Ile Val Tyr Leu Leu Ile Gly Tyr Leu Arg Tyr Leu
95 100 105 110

ATA AAT CGT AGG AGT TTA GGA TCT TTA AGA CAT GAT ATA GAC ATA GAA 6646
Ile Asn Arg Arg Ser Leu Gly Ser Leu Arg His Asp Ile Asp Ile Glu
115 120 125

ACA CCT CAA GAG GAA TAT TAT AGT AAT AGT GAA AGG GGT ACC ACA TTA 6694
Thr Pro Gln Glu Glu Tyr Tyr Ser Asn Ser Glu Arg Gly Thr Thr Leu
130 135 140

AAT CAA AAA TAT GCG AGA AGA TGT TGT GTT AGC ACA CTT ATT ATG TAT 6742
Asn Gln Lys Tyr Ala Arg Arg Cys Cys Val Ser Thr Leu Ile Met Tyr
145 150 155

TTA ATT CTT TTT GCA GTA GGC ATC TGG TGG GGA GCT AGA GCA CAA GTA 6790
Leu Ile Leu Phe Ala Val Gly Ile Trp Trp Gly Ala Arg Ala Gln Val
160 165 170

GTG TGG AGA CTT CCC CCT TTA GTA GTT CCA GTA GAA GAA TCA GAA ATA 6838
Val Trp Arg Leu Pro Pro Leu Val Val Pro Val Glu Glu Ser Glu Ile
175 180 185 190

ATT TTT TGG GAT TGT TGG GCA CCA GAA GAA CCC GCC TGT CAA GAC TTT 6886
Ile Phe Trp Asp Cys Trp Ala Pro Glu Glu Pro Ala Cys Gln Asp Phe
195 200 205

CTT GGG GCA ATG ATA CAT CTA AAA GCT AGT ACG AAT ATA AGT ATA CAA 6934
Leu Gly Ala Met Ile His Leu Lys Ala Ser Thr Asn Ile Ser Ile Gln
210 215 220

GAG GGA CCT ACC TTG GGG AAT TGG GCT AGA GAA ATA TGG GGA ACA TTA 6982
Glu Gly Pro Thr Leu Gly Asn Trp Ala Arg Glu Ile Trp Gly Thr Leu
225 230 235

TTC AAA AAG GCT ACC AGA CAA TGT AGA AGA GGT AGA ATA TGG AAA AGA 7030
Phe Lys Lys Ala Thr Arg Gln Cys Arg Arg Gly Arg Ile Trp Lys Arg
240 245 250

TGG AAT GAA ACT ATA ACA GGA CCA TTA GGA TGT GCT AAT AAC ACA TGT 7078
Trp Asn Glu Thr Ile Thr Gly Pro Leu Gly Cys Ala Asn Asn Thr Cys
255 260 265 270

TAT AAT ATT TCA GTA ATA GTA CCT GAT TAT CAA TGT TAT CTA GAC CGA 7126
Tyr Asn Ile Ser Val Ile Val Pro Asp Tyr Gln Cys Tyr Leu Asp Arg
275 280 285

GTA GAT ACT TGG TTA CAA GGG AAA GTA AAT ATA TCA TTA TGT CTA ACA 7174
Val Asp Thr Trp Leu Gln Gly Lys Val Asn Ile Ser Leu Cys Leu Thr
290 295 300

GGA GGA AAA ATG TTG TAC AAT AAA TAT ACA AAA CAA TTA AGC TAT TGT 7222
Gly Gly Lys Met Leu Tyr Asn Lys Tyr Thr Lys Gln Leu Ser Tyr Cys
305 310 315

ACA GAC CCA TTA CAA ATC CCA CTG ATC AAT TAT ACA TTT GGA CCT AAT 7270
Thr Asp Pro Leu Gln Ile Pro Leu Ile Asn Tyr Thr Phe Gly Pro Asn
320 325 330

CAA ACA TGT ATG TGG AAC ACT TCA CAA ATT CAG GAC CCT GAG ATA CCA 7318
Gln Thr Cys Met Trp Asn Thr Ser Gln Ile Gln Asp Pro Glu Ile Pro
335 340 345 350

AAA TGT GGA TGG TGG AAT CAA AGA GCC TAT TAT AAA AAT TGT AAA TGG 7366
Lys Cys Gly Trp Trp Asn Gln Arg Ala Tyr Tyr Lys Asn Cys Lys Trp
355 360 365

GAA AAA ACA GAT GTA AAG TTT CAT TGT CAA AGA ACA CAG AGT CAG CCT 7414
Glu Lys Thr Asp Val Lys Phe His Cys Gln Arg Thr Gln Ser Gln Pro
370 375 380

GGA ACA TGG CTT AGA GCA ATC TCG TCA TGG AGA CAA AGG AAT AGA TGG 7462
Gly Thr Trp Leu Arg Ala Ile Ser Ser Trp Arg Gln Arg Asn Arg Trp
385 390 395

GAA TGG AGA CCA GAT TTT GAA AGT GAA AAG GTG AAA ATA TCT CTA AAG 7510
Glu Trp Arg Pro Asp Phe Glu Ser Glu Lys Val Lys Ile Ser Leu Lys
400 405 410

TGT AAT AGC ACA AAA AAC CTA ACC TTT GCA ATG AGA AGT TCA GGA GAT 7558
Cys Asn Ser Thr Lys Asn Leu Thr Phe Ala Met Arg Ser Ser Gly Asp
415 420 425 430

TAT GGA GAA GTA ACG GGA GCT TGG ATA GAG TTT GGA TGT CAT AGA AAT 7606
Tyr Gly Glu Val Thr Gly Ala Trp Ile Glu Phe Gly Cys His Arg Asn
435 440 445

AAA TCA AAA CTT CAT GAT GAA GCA AGG TTT AGA ATT AGA TGT AGA TGG 7654
Lys Ser Lys Leu His Asp Glu Ala Arg Phe Arg Ile Arg Cys Arg Trp
450 455 460

AAT ATA GGG GAG AAT ACC TCA CTC ATT GAT ACA TGT GGA AAC ACT CAA 7702
Asn Ile Gly Glu Asn Thr Ser Leu Ile Asp Thr Cys Gly Asn Thr Gln
465 470 475

AAT GTT TCA GGG GCA AAT CCT GTA GAT TGT ACC ATG TAT GCA AAT AAA 7750
Asn Val Ser Gly Ala Asn Pro Val Asp Cys Thr Met Tyr Ala Asn Lys
480 485 490

ATG TAC AAT TGT TCT TTA CAA AAC GGG TTT ACT ATG AAG GTA GAT GAC 7798
Met Tyr Asn Cys Ser Leu Gln Asn Gly Phe Thr Met Lys Val Asp Asp
495 500 505 510

CTT ATT ATG CAT TTC AAT ATG ACA AAA GCT GTA GAA ATG TAT AAT ATT 7846
Leu Ile Met His Phe Asn Met Thr Lys Ala Val Glu Met Tyr Asn Ile
515 520 525

GCT GGA AAT TGG TCT TGT ACA TCT GAC TTG CCA CCA ACA TGG GGG TAT 7894
Ala Gly Asn Trp Ser Cys Thr Ser Asp Leu Pro Pro Thr Trp Gly Tyr
530 535 540

ATG AAT TGT AAC TGT ACA AAT AAT AGT AAT GAT AAT ACT AGA ATG GCA 7942
Met Asn Cys Asn Cys Thr Asn Asn Ser Asn Asp Asn Thr Arg Met Ala
545 550 555

TGT CCT AAC AAT CAA GGC ATC TTA AGG AAT TGG TAT AAC CCA GTA GCA 7990
Cys Pro Asn Asn Gln Gly Ile Leu Arg Asn Trp Tyr Asn Pro Val Ala
560 565 570

GGA TTA CGA CAA TCC TTG GAA AAG TAT CAA GTT GTA AAA CAA CCA GAT 8038
Gly Leu Arg Gln Ser Leu Glu Lys Tyr Gln Val Val Lys Gln Pro Asp
575 580 585 590

TAC TTA GTG GTC CCA GGG GAA GTC ATG GAA TAT AAA ACT AGA AGG AAA 8086
Tyr Leu Val Val Pro Gly Glu Val Met Glu Tyr Lys Thr Arg Arg Lys
595 600 605

AGG GCA GCT ATT CAT GTT ATG TTA GCT CTT GCA ACA GTA TTA TCT ATG 8134
Arg Ala Ala Ile His Val Met Leu Ala Leu Ala Thr Val Leu Ser Met
610 615 620

GCC GGA GCA GGG ACG GGG GCT ACT GCT ATA GGG ATG GTA ACA CAA TAT 8182
Ala Gly Ala Gly Thr Gly Ala Thr Ala Ile Gly Met Val Thr Gln Tyr
625 630 635

CAC CAA GTT CTA GCA ACC CAT CAA GAA GCT ATT GAA AAG GTG ACT GAA 8230
His Gln Val Leu Ala Thr His Gln Glu Ala Ile Glu Lys Val Thr Glu
640 645 650

GCC TTA AAG ATA AAC AAC TTG AGA TTA GTT ACA TTA GAG CAT CAA GTA 8278
Ala Leu Lys Ile Asn Asn Leu Arg Leu Val Thr Leu Glu His Gln Val
655 660 665 670

CTA GTA ATA GGA TTA AAA GTA GAA GCT ATG GAA AAA TTT TTA TAT ACA 8326
Leu Val Ile Gly Leu Lys Val Glu Ala Met Glu Lys Phe Leu Tyr Thr
675 680 685

GCT TTC GCT ATG CAA GAA TTA GGA TGT AAT CAA AAT CAA TTC TTC TGC 8374
Ala Phe Ala Met Gln Glu Leu Gly Cys Asn Gln Asn Gln Phe Phe Cys
690 695 700

AAA GTC CCT CCT GAA TTG TGG ATG AGG TAT AAT ATG TCT ATA AAT CAA 8422
Lys Val Pro Pro Glu Leu Trp Met Arg Tyr Asn Met Ser Ile Asn Gln
705 710 715

ACA ATA TGG AAT CAT GGA AAT ATA ACT TTG GGG GAA TGG TAT AAC CAA 8470
Thr Ile Trp Asn His Gly Asn Ile Thr Leu Gly Glu Trp Tyr Asn Gln
720 725 730

ACA AAA GAT TTA CAA CAA AAG TTT TAT GAA ATA ATA ATG GAC ATA GAA 8518
Thr Lys Asp Leu Gln Gln Lys Phe Tyr Glu Ile Ile Met Asp Ile Glu
735 740 745 750

CAA AAT AAT GTA CAA GGG AAA AAA GGG ATA CAA CAA TTA CAA AAG TGG 8566
Gln Asn Asn Val Gln Gly Lys Lys Gly Ile Gln Gln Leu Gln Lys Trp
755 760 765

GAA GAT TGG GTA GGA TGG ATA GGA AAT ATT CCA CAA TAC TTA AAG GGA 8614
Glu Asp Trp Val Gly Trp Ile Gly Asn Ile Pro Gln Tyr Leu Lys Gly
770 775 780

CTA TTG GGA GGT ATC TTG GGA ATA GGA TTA GGA GTG TTA TTA TTA ATT 8662
Leu Leu Gly Gly Ile Leu Gly Ile Gly Leu Gly Val Leu Leu Leu Ile
785 790 795

TTA TGT TTA CCC ACA TTG GTT GAT TGT ATA AGA AAT TGT ATC CAC AAG 8710
Leu Cys Leu Pro Thr Leu Val Asp Cys Ile Arg Asn Cys Ile His Lys
800 805 810

ATA CTA GGA TAC ACA GTA ATT GCA ATG CCT GAA GTA GAA GGA GAA GAA 8758
Ile Leu Gly Tyr Thr Val Ile Ala Met Pro Glu Val Glu Gly Glu Glu
815 820 825 830

ATA CAA CCA CAA ATG GAA TTG AGG AGA AAT GGT AGG CAA TGT GGC ATA 8806
Ile Gln Pro Gln Met Glu Leu Arg Arg Asn Gly Arg Gln Cys Gly Ile
835 840 845

TCT GAA AAA GAG GAG GAA TGATGAAGTA TCTCAGACTT ATTTTATAAG 8854
Ser Glu Lys Glu Glu Glu
850

GGAGATGCTG TGCTGAGTTC TTCCCTTTGA GGAAGGTATG TCATATGAAT CCATTTCAAA 8914

TCAAATTAAA CTAATAAAGT ATGTATTATA AGGTAAAAAG AAAAAAAGAC AAAGAAGAAG 8974

AAGAAGGAAG AAAGCCTTCA AGAATATGAT GACAGCTTTA GAAGATCGCT TTAGAAAGCT 9034

ATTTGGCACA AATTCTACAA CGGGAGACAG TACAGTGGAA TCTGACGATG AACCTCCTAA 9094

AAAAGAAAAA AGGGTGGACT GGGATGAGTA TTGGGACCCT GAAGAAATAG AAAGAATGCT 9154

TATGGACTAG TGACTGTTTA CGAACAAATG ATAAATGATG GAAACAGCTG AGCATGACTC 9214

ATAGTTAAAG CGCTAGCAGC TGCTTAACCG CAAAACCACA TCCTATGTAA AGCTTGCTGA 9274

TGACGTATAA TTTGCTCCAC TGTAAAAGTA TATAACCAGT GCTTTGTGAG ACTTCGGGGA 9334

GTCTCTCCGT TGAGGACTTT CGAGTTCTCC CTTGAGGCTC CCACAGATAC AATAAATATT 9394

TGAGATTGAA CCCTGTCAAG TATCTGTGTA ATCTTTTTTA CCTGTGAGGT CTCGGAATCC 9454

GGGCCGAGAA CTTCGCA 9471

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 450 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Gly Asn Gly Gln Gly Arg Asp Trp Lys Met Ala Ile Lys Arg Cys
1 5 10 15

Ser Asn Val Ala Val Gly Val Gly Gly Lys Ser Lys Lys Phe Gly Glu
20 25 30

Gly Asn Phe Arg Trp Ala Ile Arg Met Ala Asn Val Ser Thr Gly Arg
35 40 45

Glu Pro Gly Asp Ile Pro Glu Thr Leu Asp Gln Leu Arg Leu Val Ile
50 55 60

Cys Asp Leu Gln Glu Arg Arg Glu Lys Phe Gly Ser Ser Lys Glu Ile
65 70 75 80

Asp Met Ala Ile Val Thr Leu Lys Val Phe Ala Val Val Gly Leu Leu
85 90 95

Asn Met Thr Val Ser Thr Ala Ala Ala Ala Glu Asn Met Tyr Thr Gln
100 105 110

Met Gly Leu Asp Thr Arg Pro Ser Met Arg Glu Ala Gly Gly Lys Glu
115 120 125

Glu Ser Pro Pro Gln Ala Ser Pro Ile Gln Thr Ala Asn Gly Ala Pro
130 135 140

Gln Tyr Val Ala Leu Asp Pro Lys Met Val Ser Ile Phe Met Glu Lys
145 150 155 160

Ala Arg Glu Gly Leu Gly Gly Glu Glu Val Gln Leu Trp Phe Thr Ala
165 170 175

Phe Ser Ala Asn Leu Thr Pro Thr Asp Met Ala Thr Leu Ile Met Ala
180 185 190

Ala Pro Gly Cys Ala Ala Asp Lys Glu Ile Leu Asp Glu Ser Leu Lys
195 200 205

Gln Leu Thr Ala Glu Tyr Asp Arg Thr His Pro Pro Asp Gly Pro Arg
210 215 220

Pro Leu Pro Tyr Phe Thr Ala Ala Glu Ile Met Gly Ile Gly Leu Thr
225 230 235 240

Gln Glu Gln Gln Ala Glu Ala Arg Phe Ala Pro Ala Arg Met Gln Cys
245 250 255

Arg Ala Trp Tyr Leu Glu Ala Leu Gly Lys Leu Ala Ala Ile Lys Ala
260 265 270

Lys Ser Pro Arg Ala Val Gln Leu Arg Gln Gly Ala Lys Glu Asp Tyr
275 280 285

Ser Ser Phe Ile Asp Arg Leu Phe Ala Gln Ile Asp Gln Glu Gln Asn
290 295 300

Thr Ala Glu Val Lys Leu Tyr Leu Lys Gln Ser Leu Ser Met Ala Asn
305 310 315 320

Ala Asn Ala Glu Cys Lys Lys Ala Met Ser His Leu Lys Pro Glu Ser
325 330 335

Thr Leu Glu Glu Lys Leu Arg Ala Cys Gln Glu Val Gly Ser Pro Gly
340 345 350

Tyr Lys Met Gln Leu Leu Ala Glu Ala Leu Thr Lys Val Gln Val Val
355 360 365

Gln Ser Lys Gly Ser Gly Pro Val Cys Phe Asn Cys Lys Lys Pro Gly
370 375 380

His Leu Ala Lys Gln Cys Arg Asp Val Lys Lys Cys Asn Lys Cys Gly
385 390 395 400

Lys Pro Gly His Leu Ala Ala Lys Cys Trp Gln Gly Gly Lys Lys Asn
405 410 415

Ser Gly Asn Trp Lys Ala Gly Arg Ala Ala Ala Pro Val Asn Gln Val
420 425 430

Gln Gln Ala Val Met Pro Ser Ala Pro Pro Met Glu Glu Arg Leu Leu
435 440 445

Asp Leu
450

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 852 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Met Ala Glu Gly Phe Ala Ala Asn Arg Gln Trp Ile Gly Pro Glu Glu
1 5 10 15

Ala Glu Glu Leu Leu Asp Phe Asp Ile Ala Thr Gln Met Asn Glu Glu
20 25 30

Gly Pro Leu Asn Pro Gly Met Asn Pro Phe Arg Val Pro Gly Ile Thr
35 40 45

Asp Lys Glu Lys Gln Asp Tyr Cys Asn Ile Leu Gln Pro Lys Leu Gln
50 55 60

Asp Leu Arg Asn Glu Leu Gln Glu Val Lys Leu Glu Glu Gly Asn Ala
65 70 75 80

Gly Lys Phe Arg Arg Ala Arg Tyr Leu Arg Tyr Ser Asp Glu Asn Val
85 90 95

Leu Ser Ile Val Tyr Leu Leu Ile Gly Tyr Leu Arg Tyr Leu Ile Asn
100 105 110

Arg Arg Ser Leu Gly Ser Leu Arg His Asp Ile Asp Ile Glu Thr Pro
115 120 125

Gln Glu Glu Tyr Tyr Ser Asn Ser Glu Arg Gly Thr Thr Leu Asn Gln
130 135 140

Lys Tyr Ala Arg Arg Cys Cys Val Ser Thr Leu Ile Met Tyr Leu Ile
145 150 155 160

Leu Phe Ala Val Gly Ile Trp Trp Gly Ala Arg Ala Gln Val Val Trp
165 170 175

Arg Leu Pro Pro Leu Val Val Pro Val Glu Glu Ser Glu Ile Ile Phe
180 185 190

Trp Asp Cys Trp Ala Pro Glu Glu Pro Ala Cys Gln Asp Phe Leu Gly
195 200 205

Ala Met Ile His Leu Lys Ala Ser Thr Asn Ile Ser Ile Gln Glu Gly
210 215 220

Pro Thr Leu Gly Asn Trp Ala Arg Glu Ile Trp Gly Thr Leu Phe Lys
225 230 235 240

Lys Ala Thr Arg Gln Cys Arg Arg Gly Arg Ile Trp Lys Arg Trp Asn
245 250 255

Glu Thr Ile Thr Gly Pro Leu Gly Cys Ala Asn Asn Thr Cys Tyr Asn
260 265 270

Ile Ser Val Ile Val Pro Asp Tyr Gln Cys Tyr Leu Asp Arg Val Asp
275 280 285

Thr Trp Leu Gln Gly Lys Val Asn Ile Ser Leu Cys Leu Thr Gly Gly
290 295 300

Lys Met Leu Tyr Asn Lys Tyr Thr Lys Gln Leu Ser Tyr Cys Thr Asp
305 310 315 320

Pro Leu Gln Ile Pro Leu Ile Asn Tyr Thr Phe Gly Pro Asn Gln Thr
325 330 335

Cys Met Trp Asn Thr Ser Gln Ile Gln Asp Pro Glu Ile Pro Lys Cys
340 345 350

Gly Trp Trp Asn Gln Arg Ala Tyr Tyr Lys Asn Cys Lys Trp Glu Lys
355 360 365

Thr Asp Val Lys Phe His Cys Gln Arg Thr Gln Ser Gln Pro Gly Thr
370 375 380

Trp Leu Arg Ala Ile Ser Ser Trp Arg Gln Arg Asn Arg Trp Glu Trp
385 390 395 400

Arg Pro Asp Phe Glu Ser Glu Lys Val Lys Ile Ser Leu Lys Cys Asn
405 410 415

Ser Thr Lys Asn Leu Thr Phe Ala Met Arg Ser Ser Gly Asp Tyr Gly
420 425 430

Glu Val Thr Gly Ala Trp Ile Glu Phe Gly Cys His Arg Asn Lys Ser
435 440 445

Lys Leu His Asp Glu Ala Arg Phe Arg Ile Arg Cys Arg Trp Asn Ile
450 455 460

Gly Glu Asn Thr Ser Leu Ile Asp Thr Cys Gly Asn Thr Gln Asn Val
465 470 475 480

Ser Gly Ala Asn Pro Val Asp Cys Thr Met Tyr Ala Asn Lys Met Tyr
485 490 495

Asn Cys Ser Leu Gln Asn Gly Phe Thr Met Lys Val Asp Asp Leu Ile
500 505 510

Met His Phe Asn Met Thr Lys Ala Val Glu Met Tyr Asn Ile Ala Gly
515 520 525

Asn Trp Ser Cys Thr Ser Asp Leu Pro Pro Thr Trp Gly Tyr Met Asn
530 535 540

Cys Asn Cys Thr Asn Asn Ser Asn Asp Asn Thr Arg Met Ala Cys Pro
545 550 555 560

Asn Asn Gln Gly Ile Leu Arg Asn Trp Tyr Asn Pro Val Ala Gly Leu
565 570 575

Arg Gln Ser Leu Glu Lys Tyr Gln Val Val Lys Gln Pro Asp Tyr Leu
580 585 590

Val Val Pro Gly Glu Val Met Glu Tyr Lys Thr Arg Arg Lys Arg Ala
595 600 605

Ala Ile His Val Met Leu Ala Leu Ala Thr Val Leu Ser Met Ala Gly
610 615 620

Ala Gly Thr Gly Ala Thr Ala Ile Gly Met Val Thr Gln Tyr His Gln
625 630 635 640

Val Leu Ala Thr His Gln Glu Ala Ile Glu Lys Val Thr Glu Ala Leu
645 650 655

Lys Ile Asn Asn Leu Arg Leu Val Thr Leu Glu His Gln Val Leu Val
660 665 670

Ile Gly Leu Lys Val Glu Ala Met Glu Lys Phe Leu Tyr Thr Ala Phe
675 680 685

Ala Met Gln Glu Leu Gly Cys Asn Gln Asn Gln Phe Phe Cys Lys Val
690 695 700

Pro Pro Glu Leu Trp Met Arg Tyr Asn Met Ser Ile Asn Gln Thr Ile
705 710 715 720

Trp Asn His Gly Asn Ile Thr Leu Gly Glu Trp Tyr Asn Gln Thr Lys
725 730 735

Asp Leu Gln Gln Lys Phe Tyr Glu Ile Ile Met Asp Ile Glu Gln Asn
740 745 750

Asn Val Gln Gly Lys Lys Gly Ile Gln Gln Leu Gln Lys Trp Glu Asp
755 760 765

Trp Val Gly Trp Ile Gly Asn Ile Pro Gln Tyr Leu Lys Gly Leu Leu
770 775 780

Gly Gly Ile Leu Gly Ile Gly Leu Gly Val Leu Leu Leu Ile Leu Cys
785 790 795 800

Leu Pro Thr Leu Val Asp Cys Ile Arg Asn Cys Ile His Lys Ile Leu
805 810 815

Gly Tyr Thr Val Ile Ala Met Pro Glu Val Glu Gly Glu Glu Ile Gln
820 825 830

Pro Gln Met Glu Leu Arg Arg Asn Gly Arg Gln Cys Gly Ile Ser Glu
835 840 845

Lys Glu Glu Glu
850

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1350 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ATGGGGAACG GACAGGGGCG AGATTGGAAA ATGGCCATTA AGAGATGTAG TAATGTTGCT 60
GTAGGAGTAG GGGGGAAGAG TAAAAAATTT GGAGAAGGGA ATTTCAGATG GGCCATTAGA 120
ATGGCTAATG TATCTACAGG ACGAGAACCT GGTGATATAC CAGAGACTTT AGATCAACTA 180
AGGTTGGTTA TTTGCGATTT ACAAGAAAGA AGAGAAAAAT TTGGGTCGAG CAAAGAAATT 240
GACATGGCAA TTGTTACATT AAAAGTCTTT GCGGTAGTAG GACTTTTAAA TATGACAGTG 300
TCTACTGCTG CTGCAGCTGA AAATATGTAC ACTCAGATGG GATTAGACAC TAGACCATCT 360
ATGAGAGAAG CAGGAGGAAA AGAGGAAAGC CCTCCACAGG CATCTCCTAT TCAAACAGCA 420
AATGGAGCAC CACAATATGT AGCACTTGAC CCAAAAATGG TGTCCATTTT TATGGAAAAG 480
GCAAGAGAAG GATTAGGAGG TGAGGAAGTT CAGCTATGGT TTACTGCCTT CTCTGCAAAT 540
TTAACACCTA CTGACATGGC CACATTAATA ATGGCCGCAC CAGGGTGCGC TGCAGATAAA 600
GAAATATTGG ATGAAAGCTT AAAGCAATTG ACGGCAGAGT ATGATCGTAC CCATCCTCCT 660
GATGGACCTA GACCATTACC CTATTTTACT GCAGCAGAAA TTATGGGTAT AGGATTAACT 720
CAAGAACAAC AAGCAGAAGC AAGATTTGCA CCAGCTAGGA TGCAGTGTAG AGCATGGTAT 780
CTCGAGGCAC TAGGAAAATT GGCCGCCATA AAAGCTAAGT CTCCTCGAGC TGTGCAGTTA 840
AGACAAGGAG CTAAGGAAGA TTATTCATCC TTTATAGACA GATTGTTTGC CCAAATAGAT 900
CAAGAACAAA ATACAGCTGA AGTTAAGTTA TATTTAAAAC AGTCATTAAG CATGGCTAAT 960
GCTAATGCAG AATGTAAAAA GGCAATGAGC CACCTTAAGC CAGAAAGTAC CCTAGAAGAA 1020
AAGCTGAGAG CTTGTCAAGA AGTAGGCTCA CCAGGATATA AAATGCAACT CTTGGCAGAA 1080

GCTCTTACAA AAGTTCAAGT AGTGCAATCA AAAGGATCAG GACCAGTGTG TTTCAACTGT 1140

AAAAAACCAG GACATCTAGC AAAACAGTGT AGAGATGTGA AAAAATGTAA TAAATGTGGA 1200

AAGCCTGGTC ATTTAGCTGC CAAATGCTGG CAAGGTGGTA AAAAGAATTC GGGAAACTGG 1260

AAGGCGGGGC GAGCTGCAGC CCCAGTGAAT CAAGTGCAGC AAGCAGTAAT GCCATCTGCA 1320

CCTCCAATGG AGGAGAGACT ATTGGATTTA 1350

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 405 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..405

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
ATG GGG AAC GGA CAG GGG CGA GAT TGG AAA ATG GCC ATT AAG AGA TGT      48
Met Gly Asn Gly Gln Gly Arg Asp Trp Lys Met Ala Ile Lys Arg Cys
        855                 860                 865

AGT AAT GTT GCT GTA GGA GTA GGG GGG AAG AGT AAA AAA TTT GGA GAA      96
Ser Asn Val Ala Val Gly Val Gly Gly Lys Ser Lys Lys Phe Gly Glu
    870                 875                 880

GGG AAT TTC AGA TGG GCC ATT AGA ATG GCT AAT GTA TCT ACA GGA CGA     144
Gly Asn Phe Arg Trp Ala Ile Arg Met Ala Asn Val Ser Thr Gly Arg
885                 890                 895                 900

GAA CCT GGT GAT ATA CCA GAG ACT TTA GAT CAA CTA AGG TTG GTT ATT     192
Glu Pro Gly Asp Ile Pro Glu Thr Leu Asp Gln Leu Arg Leu Val Ile
                905                 910                 915

TGC GAT TTA CAA GAA AGA AGA GAA AAA TTT GGG TCG AGC AAA GAA ATT     240
Cys Asp Leu Gln Glu Arg Arg Glu Lys Phe Gly Ser Ser Lys Glu Ile
            920                 925                 930

GAC ATG GCA ATT GTT ACA TTA AAA GTC TTT GCG GTA GTA GGA CTT TTA     288
Asp Met Ala Ile Val Thr Leu Lys Val Phe Ala Val Val Gly Leu Leu
        935                 940                 945

AAT ATG ACA GTG TCT ACT GCT GCT GCA GCT GAA AAT ATG TAC ACT CAG     336
Asn Met Thr Val Ser Thr Ala Ala Ala Ala Glu Asn Met Tyr Thr Gln
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950 955 960

ATG GGA TTA GAC ACT AGA CCA TCT ATG AGA GAA GCA GGA GGA AAA GAG 384
Met Gly Leu Asp Thr Arg Pro Ser Met Arg Glu Ala Gly Gly Lys Glu
965 970 975 980

GAA AGC CCT CCA CAG GCA TCT 405
Glu Ser Pro Pro Gln Ala Ser
985

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 135 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Gly Asn Gly Gln Gly Arg Asp Trp Lys Met Ala Ile Lys Arg Cys
1 5 10 15

Ser Asn Val Ala Val Gly Val Gly Gly Lys Ser Lys Lys Phe Gly Glu
20 25 30

Gly Asn Phe Arg Trp Ala Ile Arg Met Ala Asn Val Ser Thr Gly Arg
35 40 45

Glu Pro Gly Asp Ile Pro Glu Thr Leu Asp Gln Leu Arg Leu Val Ile
50 55 60

Cys Asp Leu Gln Glu Arg Arg Glu Lys Phe Gly Ser Ser Lys Glu Ile
65 70 75 80

Asp Met Ala Ile Val Thr Leu Lys Val Phe Ala Val Val Gly Leu Leu
85 90 95

Asn Met Thr Val Ser Thr Ala Ala Ala Ala Glu Asn Met Tyr Thr Gln
100 105 110

Met Gly Leu Asp Thr Arg Pro Ser Met Arg Glu Ala Gly Gly Lys Glu
115 120 125

Glu Ser Pro Pro Gln Ala Ser
130 135

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 669 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..669

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
CCT ATT CAA ACA GCA AAT GGA GCA CCA CAA TAT GTA GCA CTT GAC CCA      48
Pro Ile Gln Thr Ala Asn Gly Ala Pro Gln Tyr Val Ala Leu Asp Pro
                140                 145                 150

AAA ATG GTG TCC ATT TTT ATG GAA AAG GCA AGA GAA GGA TTA GGA GGT      96
Lys Met Val Ser Ile Phe Met Glu Lys Ala Arg Glu Gly Leu Gly Gly
            155                 160                 165

GAG GAA GTT CAG CTA TGG TTT ACT GCC TTC TCT GCA AAT TTA ACA CCT     144
Glu Glu Val Gln Leu Trp Phe Thr Ala Phe Ser Ala Asn Leu Thr Pro
        170                 175                 180

ACT GAC ATG GCC ACA TTA ATA ATG GCC GCA CCA GGG TGC GCT GCA GAT     192
Thr Asp Met Ala Thr Leu Ile Met Ala Ala Pro Gly Cys Ala Ala Asp
    185                 190                 195

AAA GAA ATA TTG GAT GAA AGC TTA AAG CAA TTG ACG GCA GAG TAT GAT     240
Lys Glu Ile Leu Asp Glu Ser Leu Lys Gln Leu Thr Ala Glu Tyr Asp
200                 205                 210                 215

CGT ACC CAT CCT CCT GAT GGA CCT AGA CCA TTA CCC TAT TTT ACT GCA     288
Arg Thr His Pro Pro Asp Gly Pro Arg Pro Leu Pro Tyr Phe Thr Ala
                220                 225                 230

GCA GAA ATT ATG GGT ATA GGA TTA ACT CAA GAA CAA CAA GCA GAA GCA     336
Ala Glu Ile Met Gly Ile Gly Leu Thr Gln Glu Gln Gln Ala Glu Ala
            235                 240                 245

AGA TTT GCA CCA GCT AGG ATG CAG TGT AGA GCA TGG TAT CTC GAG GCA     384
Arg Phe Ala Pro Ala Arg Met Gln Cys Arg Ala Trp Tyr Leu Glu Ala
        250                 255                 260

CTA GGA AAA TTG GCC GCC ATA AAA GCT AAG TCT CCT CGA GCT GTG CAG     432
Leu Gly Lys Leu Ala Ala Ile Lys Ala Lys Ser Pro Arg Ala Val Gln
    265                 270                 275

TTA AGA CAA GGA GCT AAG GAA GAT TAT TCA TCC TTT ATA GAC AGA TTG     480
Leu Arg Gln Gly Ala Lys Glu Asp Tyr Ser Ser Phe Ile Asp Arg Leu
280                 285                 290                 295

TTT GCC CAA ATA GAT CAA GAA CAA AAT ACA GCT GAA GTT AAG TTA TAT     528
Phe Ala Gln Ile Asp Gln Glu Gln Asn Thr Ala Glu Val Lys Leu Tyr
```

```
            300                 305                 310

TTA AAA CAG TCA TTA AGC ATG GCT AAT GCT AAT GCA GAA TGT AAA AAG      576
Leu Lys Gln Ser Leu Ser Met Ala Asn Ala Asn Ala Glu Cys Lys Lys
            315                 320                 325

GCA ATG AGC CAC CTT AAG CCA GAA AGT ACC CTA GAA GAA AAG CTG AGA      624
Ala Met Ser His Leu Lys Pro Glu Ser Thr Leu Glu Glu Lys Leu Arg
        330                 335                 340

GCT TGT CAA GAA GTA GGC TCA CCA GGA TAT AAA ATG CAA CTC TTG          669
Ala Cys Gln Glu Val Gly Ser Pro Gly Tyr Lys Met Gln Leu Leu
    345                 350                 355
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 223 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Pro Ile Gln Thr Ala Asn Gly Ala Pro Gln Tyr Val Ala Leu Asp Pro
1               5                   10                  15

Lys Met Val Ser Ile Phe Met Glu Lys Ala Arg Glu Gly Leu Gly Gly
            20                  25                  30

Glu Glu Val Gln Leu Trp Phe Thr Ala Phe Ser Ala Asn Leu Thr Pro
        35                  40                  45

Thr Asp Met Ala Thr Leu Ile Met Ala Ala Pro Gly Cys Ala Ala Asp
    50                  55                  60

Lys Glu Ile Leu Asp Glu Ser Leu Lys Gln Leu Thr Ala Glu Tyr Asp
65                  70                  75                  80

Arg Thr His Pro Pro Asp Gly Pro Arg Pro Leu Pro Tyr Phe Thr Ala
                85                  90                  95

Ala Glu Ile Met Gly Ile Gly Leu Thr Gln Glu Gln Gln Ala Glu Ala
            100                 105                 110

Arg Phe Ala Pro Ala Arg Met Gln Cys Arg Ala Trp Tyr Leu Glu Ala
        115                 120                 125

Leu Gly Lys Leu Ala Ala Ile Lys Ala Lys Ser Pro Arg Ala Val Gln
    130                 135                 140

Leu Arg Gln Gly Ala Lys Glu Asp Tyr Ser Ser Phe Ile Asp Arg Leu
145                 150                 155                 160
```

```
Phe Ala Gln Ile Asp Gln Glu Gln Asn Thr Ala Glu Val Lys Leu Tyr
                165                 170                 175

Leu Lys Gln Ser Leu Ser Met Ala Asn Ala Asn Ala Glu Cys Lys Lys
            180                 185                 190

Ala Met Ser His Leu Lys Pro Glu Ser Thr Leu Glu Glu Lys Leu Arg
        195                 200                 205

Ala Cys Gln Glu Val Gly Ser Pro Gly Tyr Lys Met Gln Leu Leu
    210                 215                 220
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..42

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
GCA GAG TAT GAT CGT ACC CAT CCT CCT GAT GGA CCT AGA CCA                42
Ala Glu Tyr Asp Arg Thr His Pro Pro Asp Gly Pro Arg Pro
    225                 230                 235
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Ala Glu Tyr Asp Arg Thr His Pro Pro Asp Gly Pro Arg Pro
  1               5                  10
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 264 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..264

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
ACA AAA GTT CAA GTA GTG CAA TCA AAA GGA TCA GGA CCA GTG TGT TTC      48
Thr Lys Val Gln Val Val Gln Ser Lys Gly Ser Gly Pro Val Cys Phe
 15                  20                  25                  30

AAC TGT AAA AAA CCA GGA CAT CTA GCA AAA CAG TGT AGA GAT GTG AAA      96
Asn Cys Lys Lys Pro Gly His Leu Ala Lys Gln Cys Arg Asp Val Lys
                 35                  40                  45

AAA TGT AAT AAA TGT GGA AAG CCT GGT CAT TTA GCT GCC AAA TGC TGG     144
Lys Cys Asn Lys Cys Gly Lys Pro Gly His Leu Ala Ala Lys Cys Trp
             50                  55                  60

CAA GGT GGT AAA AAG AAT TCG GGA AAC TGG AAG GCG GGG CGA GCT GCA     192
Gln Gly Gly Lys Lys Asn Ser Gly Asn Trp Lys Ala Gly Arg Ala Ala
         65                  70                  75

GCC CCA GTG AAT CAA GTG CAG CAA GCA GTA ATG CCA TCT GCA CCT CCA     240
Ala Pro Val Asn Gln Val Gln Gln Ala Val Met Pro Ser Ala Pro Pro
     80                  85                  90

ATG GAG GAG AGA CTA TTG GAT TTA                                     264
Met Glu Glu Arg Leu Leu Asp Leu
 95                 100
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 88 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Thr Lys Val Gln Val Val Gln Ser Lys Gly Ser Gly Pro Val Cys Phe
  1               5                  10                  15
```

Asn Cys Lys Lys Pro Gly His Leu Ala Lys Gln Cys Arg Asp Val Lys
20 25 30

Lys Cys Asn Lys Cys Gly Lys Pro Gly His Leu Ala Ala Lys Cys Trp
35 40 45

Gln Gly Gly Lys Lys Asn Ser Gly Asn Trp Lys Ala Gly Arg Ala Ala
50 55 60

Ala Pro Val Asn Gln Val Gln Gln Ala Val Met Pro Ser Ala Pro Pro
65 70 75 80

Met Glu Glu Arg Leu Leu Asp Leu
85

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3841 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

ATGATTGGAG TAGGAGGAGG AAAGAGAGGA ACAAATTATA TCAATGTGCA TTTAGAGATT 60

AGAGATGAAA ATTATAAGAC ACAATGTATA TTTGGCAATG TTTGTGTCTT AGAAGATAAC 120

TCATTAATAC AACCATTATT AGGGAGAGAT AATATGATTA GATTCAATAT TAGGTTAGTA 180

ATGGCTCAAA TTTCTGACAA GATTCCAATA GTAAAAGTAA AAATGAAGGA TCCAAATAAA 240

GGACCTCAAA TAAAACAATG GCCATTAACA AATGAAAAAA TTGAAGCTTT AACAGAAATA 300

GTAGAAAGAC TAGAAAGAGA AGGGAAAGTA AAAAGAGCAG ATCCAAATAA CCCATGGAAT 360

ACACCAGTAT TTGCAATAAA AAAGAAAAGT GGAAAATGGA GAATGCTCAT AGATTTTAGA 420

GAATTGAACA AATTAACTGA GAAAGGGGCA GAAGTCCAGT TAGGACTCCC TCATCCTGCT 480

GGATTAAAAA TGAAAAAACA AGTTACTGTG CTAGATATAG GAGATGCATA CTTCACTATT 540

CCCTTGGATC CAGACTATGC TCCCTATACT GCATTCACAT TACCTAGAAA GAATAATGCA 600

GGACCAGGGA GGAGATATGT ATGGTGCAGT TTACCACAGG GGTGGGTTCT AAGCCCATTG 660

ATATATCAAA GTACTTTAGA TAATATAATA CAACCTTTTA TTAGACAAAA TCCTGAGTTA 720

GATATTTATC AATATATGGA TGACATTTAT ATAGGATCAA ACTTAAGTAA AAAGGAGCAT 780

AAAGAAAAAG TAGAAGAATT AAGAAAATTG TTATTATGGT GGGGATTTGA AACCCCGGAA 840

GACAAATTAC AAGAAGAGCC CCCATATAAG TGGATGGGCT ATGAATTACA TCCATTAACA 900

TGGTCAATAC AGCAAAAACA ATTAGAAATT CCAGAAAGAC CCACATTAAA TGAACTGCAG 960

AAATTAGCAG GTAAGATAAA CTGGGCCAGT CAAACTATCC CAGACTTAAG TATAAAAGAA 1020

CTAACTAACA TGATGAGAGG AGATCAGAAG TTAGACTCAA TAAGAGAATG GACTGTGGAA 1080

GCCAAGAGAG AAGTACAAAA AGCTAAGGAA GCTATTGAGA TGCAAGCACA GCTAAATTAT 1140

TATGATCCCC ACCGAGAATT ATATGCAAAA TTAAGTTTAG TGGGACCACA TCAAATATGT 1200

TATCAAGTGT ATCATAAGAA CCCAGAATGT ATTTTATGGT ATGGTAAGAT GAATAGACAA 1260

AAGAAAAAGG CAGAAAATAC CTGTGATATA GCTCTAAGGG CATGTTATAA AATAAGAGAA 1320

GAATCTATTA TAAGAATAGG AAAAGAACCA ATATATGAAA TACCTACTTC TAGAGAAGCC 1380

TGGGAGTCAA ATTTAATTAA TTCACCATAT CTTAAGGCCC CACCTCCTGA GGTAGAATAT 1440

ATCCATGCTG CTGTGAATAT AAAAAGAGCA TTAAGTATGA TAAAAGATGT TCCAATACCA 1500

GAAGCAGAAA CGTGGTATAT AGATGGAGGC AGAAAGCTAG GAAAAGCAGC AAAAGCAGCC 1560

TATTGGACAG ATACAGGGAA GTGGCAAGTA ATGGAGTTAG AAGGCAGTAA TCAGAAGGCA 1620

GAAGTACAAG CATTATTATT GGCATTAAAA GCAGGATCAG AGGAAATGAA TATTATAACA 1680

GATTCACAAT ATGTTATAAA TATTATTCTT CAACAACCAG ATATGATGGA GGGAATCTGG 1740

CAAGAAGTTT TAGAAGAATT GGAGAAAAAA ACAGCAATAT TTATAGATTG GGTCCCAGGA 1800

CATAAAGGTA TTCCAGGAAA TGAGGAAGTA GATAAGCTTT GTCAAACAAT GATGATAATA 1860

GAAGGGGATG GGATATTAGA TAAAAGGTCA GAAGATGCGG GATATGATTT ATTGGCTGCA 1920

AAAGAAATAC ATTTATTGCC AGGAGAGGTA AAAGTAATAC CAACAGGGGT AAAGCTAATG 1980

CTGCCTAAAG GACATTGGGG ACTAATAATG GGAAGAAGCT CGATAGGGAG TAAAGGATTG 2040

GATGTATTAG GAGGGGTAAT AGATGAAGGA TATCGAGGTG AAATTGGAGT AATAATGATT 2100

AATGTATCAA GAAAATCAAT CACCTTAATG GAACAACAAA AGATAGCACA ATTAATAATA 2160

TTGCCTTGTA AACATGAAGT ATTAGAACAA GGAAAAGTTG TAATGGATTC AGAGAGAGGA 2220

GACAAAGGTT ATGGGTCAAC AGGAGTATTC TCCTCTTGGG TTGACAGGAT TGAGGAAGCA 2280

GAAATAAATC ATGAAAAATT TCACTCAGAT CCACAATACT TAAGGACTGA ATTTAATTTA 2340

CCCAAGATGG TTGCAGAAGA GATAAGACGA AAGTGCCCTG TATGTAGAAT CAGAGGAGAA 2400

CAAGTGGGAG GACAATTGAA AATAGGGCCT GGAATATGGC AAGTGGATTG CACACACTTT 2460

AATAGTAAGA TAATCATTGT AGCAGTACAT GTGGAATCAG GATTTTTATG GGCACAGATA 2520

ATTCCACAGG AGACTGCAGA TTGTACAGTC AAGGCTCTTC TGCAACTTAT ATGTGCTCAT 2580

AATGTTACAG AATTACAAAC AGACAATGGA CCAAATTTTA AAAATCAGAA AATGGAAGGT 2640

TTATTAAATT TTATGGGAAT AAAACATAAA TTAGGGATAC CAGGTAACCC ACAATCACAG 2700

GCATTAGTGG AAAATGCTAA TAACACATTA AAAGCTTGGA TTCAAAAATT CCTACCAGAG 2760

ACTACCTCTC TGGATAATGC TCTGGCCCTA GCCCTGTATA GTCTCAACTT TAAACAAAGG 2820

GGTAGACTAG GAAGGATGGC CCCTTATGAA TTATACATAC AACAAGAATC ATTAAGAATA 2880

CAAGACTATT TTTCGCAGAT TCCACAAAAG TTAATGATGC AGTGGGTGTA TTACAAAGAT 2940

CAAAAAGACA AAAAATGGAA GGGACCAATG AGAGTGGAAT ATTGGGGACA AGGATCAGTA 3000

TTATTAAAGG ATGAAGAGAA GGGATATTTT CTTGTACCTA GGAGACACAT AAGAAGAGTC 3060

CCAGAACCCT GCACTCTTCC TGAAGGGGAT GAGTGACGAA GATTGGCAGG TAAGTAGAAG 3120

ACTCTTTGCA GTGCTCCAAG GAGGAGTACG TAGTGCTATG CTATACATAT CTAGACTACC 3180

TCCGGACGAA AGAGAAAGGT ATAAAAAAGA CTTTAAGAAA AGGCTTTTGG AAAAGGAAAC 3240

AGGATTCATA CAGAGATTAA GAAAAGCGGA AGGAATAAGG TGGAGCTTCC ATACTAGAGA 3300

TTATTATATA GGATATGTAA GAGAGATGGT GGCCGGATCT AGTCTACCAG ATAGTTTAAG 3360

ACTGTATATT TATATAAGCA ATCCATTGTG GCACTGGTCA TACCGTCCTG GCCTGACAAA 3420

TTTTAATACA GAATGGCCTT TTGTGAATAT GTGGATAAAG ACAGGATTCA TGTGGGATGA 3480

TATTGAAAGC CAGAATATTT GCAAAGGAGG AGAGATTTCA CATGGATGGG GACCTGGAAT 3540

GGTGGGAATT GTGATAAAAG CTTTTAGTTG TGGAGAAAGA AAGATTGAGG CTACTCCTGT 3600

AATGATTATA AGAGGAGAAA TAGATCCAAA AAAATGGTGT GGAGATTGTT GGAATTTGAT 3660

GTGTCTTAGG AACTCACCTC CACAGACTTT ACAAAGACTT GCTATGTTGG CATGTGGCGT 3720

GCCGGCTAAG GAGTGGCGAG GATGCTGTAA TCAACGCTTT GTTTCTCCTT ACAGAACGCC 3780

TGCTGATTTG GAGGTCATTC AATCCAAGCC CAGCTGGAGT CTATTATGGT CAGGGAGCCT 3840

A 3841

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3093 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..3093

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
ATG ATT GGA GTA GGA GGA GGA AAG AGA GGA ACA AAT TAT ATC AAT GTG      48
Met Ile Gly Val Gly Gly Gly Lys Arg Gly Thr Asn Tyr Ile Asn Val
     90                  95                 100

CAT TTA GAG ATT AGA GAT GAA AAT TAT AAG ACA CAA TGT ATA TTT GGC      96
His Leu Glu Ile Arg Asp Glu Asn Tyr Lys Thr Gln Cys Ile Phe Gly
105                 110                 115                 120

AAT GTT TGT GTC TTA GAA GAT AAC TCA TTA ATA CAA CCA TTA TTA GGG     144
Asn Val Cys Val Leu Glu Asp Asn Ser Leu Ile Gln Pro Leu Leu Gly
                125                 130                 135

AGA GAT AAT ATG ATT AGA TTC AAT ATT AGG TTA GTA ATG GCT CAA ATT     192
Arg Asp Asn Met Ile Arg Phe Asn Ile Arg Leu Val Met Ala Gln Ile
            140                 145                 150

TCT GAC AAG ATT CCA ATA GTA AAA GTA AAA ATG AAG GAT CCA AAT AAA     240
Ser Asp Lys Ile Pro Ile Val Lys Val Lys Met Lys Asp Pro Asn Lys
        155                 160                 165

GGA CCT CAA ATA AAA CAA TGG CCA TTA ACA AAT GAA AAA ATT GAA GCT     288
Gly Pro Gln Ile Lys Gln Trp Pro Leu Thr Asn Glu Lys Ile Glu Ala
    170                 175                 180

TTA ACA GAA ATA GTA GAA AGA CTA GAA AGA GAA GGG AAA GTA AAA AGA     336
Leu Thr Glu Ile Val Glu Arg Leu Glu Arg Glu Gly Lys Val Lys Arg
185                 190                 195                 200

GCA GAT CCA AAT AAC CCA TGG AAT ACA CCA GTA TTT GCA ATA AAA AAG     384
Ala Asp Pro Asn Asn Pro Trp Asn Thr Pro Val Phe Ala Ile Lys Lys
                205                 210                 215

AAA AGT GGA AAA TGG AGA ATG CTC ATA GAT TTT AGA GAA TTG AAC AAA     432
Lys Ser Gly Lys Trp Arg Met Leu Ile Asp Phe Arg Glu Leu Asn Lys
            220                 225                 230

TTA ACT GAG AAA GGG GCA GAA GTC CAG TTA GGA CTC CCT CAT CCT GCT     480
Leu Thr Glu Lys Gly Ala Glu Val Gln Leu Gly Leu Pro His Pro Ala
```

235 240 245

GGA TTA AAA ATG AAA AAA CAA GTT ACT GTG CTA GAT ATA GGA GAT GCA 528
Gly Leu Lys Met Lys Lys Gln Val Thr Val Leu Asp Ile Gly Asp Ala
250 255 260

TAC TTC ACT ATT CCC TTG GAT CCA GAC TAT GCT CCC TAT ACT GCA TTC 576
Tyr Phe Thr Ile Pro Leu Asp Pro Asp Tyr Ala Pro Tyr Thr Ala Phe
265 270 275 280

ACA TTA CCT AGA AAG AAT AAT GCA GGA CCA GGG AGG AGA TAT GTA TGG 624
Thr Leu Pro Arg Lys Asn Asn Ala Gly Pro Gly Arg Arg Tyr Val Trp
285 290 295

TGC AGT TTA CCA CAG GGG TGG GTT CTA AGC CCA TTG ATA TAT CAA AGT 672
Cys Ser Leu Pro Gln Gly Trp Val Leu Ser Pro Leu Ile Tyr Gln Ser
300 305 310

ACT TTA GAT AAT ATA ATA CAA CCT TTT ATT AGA CAA AAT CCT GAG TTA 720
Thr Leu Asp Asn Ile Ile Gln Pro Phe Ile Arg Gln Asn Pro Glu Leu
315 320 325

GAT ATT TAT CAA TAT ATG GAT GAC ATT TAT ATA GGA TCA AAC TTA AGT 768
Asp Ile Tyr Gln Tyr Met Asp Asp Ile Tyr Ile Gly Ser Asn Leu Ser
330 335 340

AAA AAG GAG CAT AAA GAA AAA GTA GAA GAA TTA AGA AAA TTG TTA TTA 816
Lys Lys Glu His Lys Glu Lys Val Glu Glu Leu Arg Lys Leu Leu Leu
345 350 355 360

TGG TGG GGA TTT GAA ACC CCG GAA GAC AAA TTA CAA GAA GAG CCC CCA 864
Trp Trp Gly Phe Glu Thr Pro Glu Asp Lys Leu Gln Glu Glu Pro Pro
365 370 375

TAT AAG TGG ATG GGC TAT GAA TTA CAT CCA TTA ACA TGG TCA ATA CAG 912
Tyr Lys Trp Met Gly Tyr Glu Leu His Pro Leu Thr Trp Ser Ile Gln
380 385 390

CAA AAA CAA TTA GAA ATT CCA GAA AGA CCC ACA TTA AAT GAA CTG CAG 960
Gln Lys Gln Leu Glu Ile Pro Glu Arg Pro Thr Leu Asn Glu Leu Gln
395 400 405

AAA TTA GCA GGT AAG ATA AAC TGG GCC AGT CAA ACT ATC CCA GAC TTA 1008
Lys Leu Ala Gly Lys Ile Asn Trp Ala Ser Gln Thr Ile Pro Asp Leu
410 415 420

AGT ATA AAA GAA CTA ACT AAC ATG ATG AGA GGA GAT CAG AAG TTA GAC 1056
Ser Ile Lys Glu Leu Thr Asn Met Met Arg Gly Asp Gln Lys Leu Asp
425 430 435 440

TCA ATA AGA GAA TGG ACT GTG GAA GCC AAG AGA GAA GTA CAA AAA GCT 1104
Ser Ile Arg Glu Trp Thr Val Glu Ala Lys Arg Glu Val Gln Lys Ala
445 450 455

AAG GAA GCT ATT GAG ATG CAA GCA CAG CTA AAT TAT TAT GAT CCC CAC 1152
Lys Glu Ala Ile Glu Met Gln Ala Gln Leu Asn Tyr Tyr Asp Pro His

460 465 470

CGA GAA TTA TAT GCA AAA TTA AGT TTA GTG GGA CCA CAT CAA ATA TGT 1200
Arg Glu Leu Tyr Ala Lys Leu Ser Leu Val Gly Pro His Gln Ile Cys
475 480 485

TAT CAA GTG TAT CAT AAG AAC CCA GAA TGT ATT TTA TGG TAT GGT AAG 1248
Tyr Gln Val Tyr His Lys Asn Pro Glu Cys Ile Leu Trp Tyr Gly Lys
490 495 500

ATG AAT AGA CAA AAG AAA AAG GCA GAA AAT ACC TGT GAT ATA GCT CTA 1296
Met Asn Arg Gln Lys Lys Lys Ala Glu Asn Thr Cys Asp Ile Ala Leu
505 510 515 520

AGG GCA TGT TAT AAA ATA AGA GAA GAA TCT ATT ATA AGA ATA GGA AAA 1344
Arg Ala Cys Tyr Lys Ile Arg Glu Glu Ser Ile Ile Arg Ile Gly Lys
525 530 535

GAA CCA ATA TAT GAA ATA CCT ACT TCT AGA GAA GCC TGG GAG TCA AAT 1392
Glu Pro Ile Tyr Glu Ile Pro Thr Ser Arg Glu Ala Trp Glu Ser Asn
540 545 550

TTA ATT AAT TCA CCA TAT CTT AAG GCC CCA CCT CCT GAG GTA GAA TAT 1440
Leu Ile Asn Ser Pro Tyr Leu Lys Ala Pro Pro Pro Glu Val Glu Tyr
555 560 565

ATC CAT GCT GCT GTG AAT ATA AAA AGA GCA TTA AGT ATG ATA AAA GAT 1488
Ile His Ala Ala Val Asn Ile Lys Arg Ala Leu Ser Met Ile Lys Asp
570 575 580

GTT CCA ATA CCA GAA GCA GAA ACG TGG TAT ATA GAT GGA GGC AGA AAG 1536
Val Pro Ile Pro Glu Ala Glu Thr Trp Tyr Ile Asp Gly Gly Arg Lys
585 590 595 600

CTA GGA AAA GCA GCA AAA GCA GCC TAT TGG ACA GAT ACA GGG AAG TGG 1584
Leu Gly Lys Ala Ala Lys Ala Ala Tyr Trp Thr Asp Thr Gly Lys Trp
605 610 615

CAA GTA ATG GAG TTA GAA GGC AGT AAT CAG AAG GCA GAA GTA CAA GCA 1632
Gln Val Met Glu Leu Glu Gly Ser Asn Gln Lys Ala Glu Val Gln Ala
620 625 630

TTA TTA TTG GCA TTA AAA GCA GGA TCA GAG GAA ATG AAT ATT ATA ACA 1680
Leu Leu Leu Ala Leu Lys Ala Gly Ser Glu Glu Met Asn Ile Ile Thr
635 640 645

GAT TCA CAA TAT GTT ATA AAT ATT ATT CTT CAA CAA CCA GAT ATG ATG 1728
Asp Ser Gln Tyr Val Ile Asn Ile Ile Leu Gln Gln Pro Asp Met Met
650 655 660

GAG GGA ATC TGG CAA GAA GTT TTA GAA GAA TTG GAG AAA AAA ACA GCA 1776
Glu Gly Ile Trp Gln Glu Val Leu Glu Glu Leu Glu Lys Lys Thr Ala
665 670 675 680

ATA TTT ATA GAT TGG GTC CCA GGA CAT AAA GGT ATT CCA GGA AAT GAG 1824
Ile Phe Ile Asp Trp Val Pro Gly His Lys Gly Ile Pro Gly Asn Glu

685 690 695

GAA GTA GAT AAG CTT TGT CAA ACA ATG ATG ATA ATA GAA GGG GAT GGG 1872
Glu Val Asp Lys Leu Cys Gln Thr Met Met Ile Ile Glu Gly Asp Gly
700 705 710

ATA TTA GAT AAA AGG TCA GAA GAT GCG GGA TAT GAT TTA TTG GCT GCA 1920
Ile Leu Asp Lys Arg Ser Glu Asp Ala Gly Tyr Asp Leu Leu Ala Ala
715 720 725

AAA GAA ATA CAT TTA TTG CCA GGA GAG GTA AAA GTA ATA CCA ACA GGG 1968
Lys Glu Ile His Leu Leu Pro Gly Glu Val Lys Val Ile Pro Thr Gly
730 735 740

GTA AAG CTA ATG CTG CCT AAA GGA CAT TGG GGA CTA ATA ATG GGA AGA 2016
Val Lys Leu Met Leu Pro Lys Gly His Trp Gly Leu Ile Met Gly Arg
745 750 755 760

AGC TCG ATA GGG AGT AAA GGA TTG GAT GTA TTA GGA GGG GTA ATA GAT 2064
Ser Ser Ile Gly Ser Lys Gly Leu Asp Val Leu Gly Gly Val Ile Asp
765 770 775

GAA GGA TAT CGA GGT GAA ATT GGA GTA ATA ATG ATT AAT GTA TCA AGA 2112
Glu Gly Tyr Arg Gly Glu Ile Gly Val Ile Met Ile Asn Val Ser Arg
780 785 790

AAA TCA ATC ACC TTA ATG GAA CAA CAA AAG ATA GCA CAA TTA ATA ATA 2160
Lys Ser Ile Thr Leu Met Glu Gln Gln Lys Ile Ala Gln Leu Ile Ile
795 800 805

TTG CCT TGT AAA CAT GAA GTA TTA GAA CAA GGA AAA GTT GTA ATG GAT 2208
Leu Pro Cys Lys His Glu Val Leu Glu Gln Gly Lys Val Val Met Asp
810 815 820

TCA GAG AGA GGA GAC AAA GGT TAT GGG TCA ACA GGA GTA TTC TCC TCT 2256
Ser Glu Arg Gly Asp Lys Gly Tyr Gly Ser Thr Gly Val Phe Ser Ser
825 830 835 840

TGG GTT GAC AGG ATT GAG GAA GCA GAA ATA AAT CAT GAA AAA TTT CAC 2304
Trp Val Asp Arg Ile Glu Glu Ala Glu Ile Asn His Glu Lys Phe His
845 850 855

TCA GAT CCA CAA TAC TTA AGG ACT GAA TTT AAT TTA CCC AAG ATG GTT 2352
Ser Asp Pro Gln Tyr Leu Arg Thr Glu Phe Asn Leu Pro Lys Met Val
860 865 870

GCA GAA GAG ATA AGA CGA AAG TGC CCT GTA TGT AGA ATC AGA GGA GAA 2400
Ala Glu Glu Ile Arg Arg Lys Cys Pro Val Cys Arg Ile Arg Gly Glu
875 880 885

CAA GTG GGA GGA CAA TTG AAA ATA GGG CCT GGA ATA TGG CAA GTG GAT 2448
Gln Val Gly Gly Gln Leu Lys Ile Gly Pro Gly Ile Trp Gln Val Asp
890 895 900

TGC ACA CAC TTT AAT AGT AAG ATA ATC ATT GTA GCA GTA CAT GTG GAA 2496
Cys Thr His Phe Asn Ser Lys Ile Ile Ile Val Ala Val His Val Glu

905 910 915 920

TCA GGA TTT TTA TGG GCA CAG ATA ATT CCA CAG GAG ACT GCA GAT TGT 2544
Ser Gly Phe Leu Trp Ala Gln Ile Ile Pro Gln Glu Thr Ala Asp Cys
925 930 935

ACA GTC AAG GCT CTT CTG CAA CTT ATA TGT GCT CAT AAT GTT ACA GAA 2592
Thr Val Lys Ala Leu Leu Gln Leu Ile Cys Ala His Asn Val Thr Glu
940 945 950

TTA CAA ACA GAC AAT GGA CCA AAT TTT AAA AAT CAG AAA ATG GAA GGT 2640
Leu Gln Thr Asp Asn Gly Pro Asn Phe Lys Asn Gln Lys Met Glu Gly
955 960 965

TTA TTA AAT TTT ATG GGA ATA AAA CAT AAA TTA GGG ATA CCA GGT AAC 2688
Leu Leu Asn Phe Met Gly Ile Lys His Lys Leu Gly Ile Pro Gly Asn
970 975 980

CCA CAA TCA CAG GCA TTA GTG GAA AAT GCT AAT AAC ACA TTA AAA GCT 2736
Pro Gln Ser Gln Ala Leu Val Glu Asn Ala Asn Asn Thr Leu Lys Ala
985 990 995 1000

TGG ATT CAA AAA TTC CTA CCA GAG ACT ACC TCT CTG GAT AAT GCT CTG 2784
Trp Ile Gln Lys Phe Leu Pro Glu Thr Thr Ser Leu Asp Asn Ala Leu
1005 1010 1015

GCC CTA GCC CTG TAT AGT CTC AAC TTT AAA CAA AGG GGT AGA CTA GGA 2832
Ala Leu Ala Leu Tyr Ser Leu Asn Phe Lys Gln Arg Gly Arg Leu Gly
1020 1025 1030

AGG ATG GCC CCT TAT GAA TTA TAC ATA CAA CAA GAA TCA TTA AGA ATA 2880
Arg Met Ala Pro Tyr Glu Leu Tyr Ile Gln Gln Glu Ser Leu Arg Ile
1035 1040 1045

CAA GAC TAT TTT TCG CAG ATT CCA CAA AAG TTA ATG ATG CAG TGG GTG 2928
Gln Asp Tyr Phe Ser Gln Ile Pro Gln Lys Leu Met Met Gln Trp Val
1050 1055 1060

TAT TAC AAA GAT CAA AAA GAC AAA AAA TGG AAG GGA CCA ATG AGA GTG 2976
Tyr Tyr Lys Asp Gln Lys Asp Lys Lys Trp Lys Gly Pro Met Arg Val
1065 1070 1075 1080

GAA TAT TGG GGA CAA GGA TCA GTA TTA TTA AAG GAT GAA GAG AAG GGA 3024
Glu Tyr Trp Gly Gln Gly Ser Val Leu Leu Lys Asp Glu Glu Lys Gly
1085 1090 1095

TAT TTT CTT GTA CCT AGG AGA CAC ATA AGA AGA GTC CCA GAA CCC TGC 3072
Tyr Phe Leu Val Pro Arg Arg His Ile Arg Arg Val Pro Glu Pro Cys
1100 1105 1110

ACT CTT CCT GAA GGG GAT GAG 3093
Thr Leu Pro Glu Gly Asp Glu
1115

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1031 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
Met Ile Gly Val Gly Gly Gly Lys Arg Gly Thr Asn Tyr Ile Asn Val
1               5                   10                  15

His Leu Glu Ile Arg Asp Glu Asn Tyr Lys Thr Gln Cys Ile Phe Gly
            20                  25                  30

Asn Val Cys Val Leu Glu Asp Asn Ser Leu Ile Gln Pro Leu Leu Gly
        35                  40                  45

Arg Asp Asn Met Ile Arg Phe Asn Ile Arg Leu Val Met Ala Gln Ile
    50                  55                  60

Ser Asp Lys Ile Pro Ile Val Lys Val Lys Met Lys Asp Pro Asn Lys
65                  70                  75                  80

Gly Pro Gln Ile Lys Gln Trp Pro Leu Thr Asn Glu Lys Ile Glu Ala
                85                  90                  95

Leu Thr Glu Ile Val Glu Arg Leu Glu Arg Glu Gly Lys Val Lys Arg
            100                 105                 110

Ala Asp Pro Asn Asn Pro Trp Asn Thr Pro Val Phe Ala Ile Lys Lys
        115                 120                 125

Lys Ser Gly Lys Trp Arg Met Leu Ile Asp Phe Arg Glu Leu Asn Lys
    130                 135                 140

Leu Thr Glu Lys Gly Ala Glu Val Gln Leu Gly Leu Pro His Pro Ala
145                 150                 155                 160

Gly Leu Lys Met Lys Lys Gln Val Thr Val Leu Asp Ile Gly Asp Ala
                165                 170                 175

Tyr Phe Thr Ile Pro Leu Asp Pro Asp Tyr Ala Pro Tyr Thr Ala Phe
            180                 185                 190

Thr Leu Pro Arg Lys Asn Asn Ala Gly Pro Gly Arg Arg Tyr Val Trp
        195                 200                 205

Cys Ser Leu Pro Gln Gly Trp Val Leu Ser Pro Leu Ile Tyr Gln Ser
    210                 215                 220

Thr Leu Asp Asn Ile Ile Gln Pro Phe Ile Arg Gln Asn Pro Glu Leu
225                 230                 235                 240
```

Asp Ile Tyr Gln Tyr Met Asp Asp Ile Tyr Ile Gly Ser Asn Leu Ser
245 250 255

Lys Lys Glu His Lys Glu Lys Val Glu Glu Leu Arg Lys Leu Leu Leu
260 265 270

Trp Trp Gly Phe Glu Thr Pro Glu Asp Lys Leu Gln Glu Glu Pro Pro
275 280 285

Tyr Lys Trp Met Gly Tyr Glu Leu His Pro Leu Thr Trp Ser Ile Gln
290 295 300

Gln Lys Gln Leu Glu Ile Pro Glu Arg Pro Thr Leu Asn Glu Leu Gln
305 310 315 320

Lys Leu Ala Gly Lys Ile Asn Trp Ala Ser Gln Thr Ile Pro Asp Leu
325 330 335

Ser Ile Lys Glu Leu Thr Asn Met Met Arg Gly Asp Gln Lys Leu Asp
340 345 350

Ser Ile Arg Glu Trp Thr Val Glu Ala Lys Arg Glu Val Gln Lys Ala
355 360 365

Lys Glu Ala Ile Glu Met Gln Ala Gln Leu Asn Tyr Tyr Asp Pro His
370 375 380

Arg Glu Leu Tyr Ala Lys Leu Ser Leu Val Gly Pro His Gln Ile Cys
385 390 395 400

Tyr Gln Val Tyr His Lys Asn Pro Glu Cys Ile Leu Trp Tyr Gly Lys
405 410 415

Met Asn Arg Gln Lys Lys Lys Ala Glu Asn Thr Cys Asp Ile Ala Leu
420 425 430

Arg Ala Cys Tyr Lys Ile Arg Glu Glu Ser Ile Ile Arg Ile Gly Lys
435 440 445

Glu Pro Ile Tyr Glu Ile Pro Thr Ser Arg Glu Ala Trp Glu Ser Asn
450 455 460

Leu Ile Asn Ser Pro Tyr Leu Lys Ala Pro Pro Pro Glu Val Glu Tyr
465 470 475 480

Ile His Ala Ala Val Asn Ile Lys Arg Ala Leu Ser Met Ile Lys Asp
485 490 495

Val Pro Ile Pro Glu Ala Glu Thr Trp Tyr Ile Asp Gly Gly Arg Lys
500 505 510

Leu Gly Lys Ala Ala Lys Ala Ala Tyr Trp Thr Asp Thr Gly Lys Trp
515 520 525

Gln Val Met Glu Leu Glu Gly Ser Asn Gln Lys Ala Glu Val Gln Ala
530 535 540

Leu Leu Leu Ala Leu Lys Ala Gly Ser Glu Glu Met Asn Ile Ile Thr
545 550 555 560

Asp Ser Gln Tyr Val Ile Asn Ile Ile Leu Gln Gln Pro Asp Met Met
565 570 575

Glu Gly Ile Trp Gln Glu Val Leu Glu Glu Leu Glu Lys Lys Thr Ala
580 585 590

Ile Phe Ile Asp Trp Val Pro Gly His Lys Gly Ile Pro Gly Asn Glu
595 600 605

Glu Val Asp Lys Leu Cys Gln Thr Met Met Ile Ile Glu Gly Asp Gly
610 615 620

Ile Leu Asp Lys Arg Ser Glu Asp Ala Gly Tyr Asp Leu Leu Ala Ala
625 630 635 640

Lys Glu Ile His Leu Leu Pro Gly Glu Val Lys Val Ile Pro Thr Gly
645 650 655

Val Lys Leu Met Leu Pro Lys Gly His Trp Gly Leu Ile Met Gly Arg
660 665 670

Ser Ser Ile Gly Ser Lys Gly Leu Asp Val Leu Gly Gly Val Ile Asp
675 680 685

Glu Gly Tyr Arg Gly Glu Ile Gly Val Ile Met Ile Asn Val Ser Arg
690 695 700

Lys Ser Ile Thr Leu Met Glu Gln Gln Lys Ile Ala Gln Leu Ile Ile
705 710 715 720

Leu Pro Cys Lys His Glu Val Leu Glu Gln Gly Lys Val Val Met Asp
725 730 735

Ser Glu Arg Gly Asp Lys Gly Tyr Gly Ser Thr Gly Val Phe Ser Ser
740 745 750

Trp Val Asp Arg Ile Glu Glu Ala Glu Ile Asn His Glu Lys Phe His
755 760 765

Ser Asp Pro Gln Tyr Leu Arg Thr Glu Phe Asn Leu Pro Lys Met Val
770 775 780

Ala Glu Glu Ile Arg Arg Lys Cys Pro Val Cys Arg Ile Arg Gly Glu
785 790 795 800

Gln Val Gly Gly Gln Leu Lys Ile Gly Pro Gly Ile Trp Gln Val Asp
805 810 815

Cys Thr His Phe Asn Ser Lys Ile Ile Ile Val Ala Val His Val Glu
820 825 830

Ser Gly Phe Leu Trp Ala Gln Ile Ile Pro Gln Glu Thr Ala Asp Cys
835 840 845

Thr Val Lys Ala Leu Leu Gln Leu Ile Cys Ala His Asn Val Thr Glu
850 855 860

Leu Gln Thr Asp Asn Gly Pro Asn Phe Lys Asn Gln Lys Met Glu Gly
865 870 875 880

Leu Leu Asn Phe Met Gly Ile Lys His Lys Leu Gly Ile Pro Gly Asn
885 890 895

Pro Gln Ser Gln Ala Leu Val Glu Asn Ala Asn Asn Thr Leu Lys Ala
900 905 910

Trp Ile Gln Lys Phe Leu Pro Glu Thr Thr Ser Leu Asp Asn Ala Leu
915 920 925

Ala Leu Ala Leu Tyr Ser Leu Asn Phe Lys Gln Arg Gly Arg Leu Gly
930 935 940

Arg Met Ala Pro Tyr Glu Leu Tyr Ile Gln Gln Glu Ser Leu Arg Ile
945 950 955 960

Gln Asp Tyr Phe Ser Gln Ile Pro Gln Lys Leu Met Met Gln Trp Val
965 970 975

Tyr Tyr Lys Asp Gln Lys Asp Lys Lys Trp Lys Gly Pro Met Arg Val
980 985 990

Glu Tyr Trp Gly Gln Gly Ser Val Leu Leu Lys Asp Glu Glu Lys Gly
995 1000 1005

Tyr Phe Leu Val Pro Arg Arg His Ile Arg Arg Val Pro Glu Pro Cys
1010 1015 1020

Thr Leu Pro Glu Gly Asp Glu
1025 1030

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 753 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..753

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ATG ATT GAC GAA GAT TGG CAG GTA AGT AGA AGA CTC TTT GCA GTG CTC 48
Met Ile Asp Glu Asp Trp Gln Val Ser Arg Arg Leu Phe Ala Val Leu

1035 1040 1045

CAA GGA GGA GTA CGT AGT GCT ATG CTA TAC ATA TCT AGA CTA CCT CCG 96
Gln Gly Gly Val Arg Ser Ala Met Leu Tyr Ile Ser Arg Leu Pro Pro
1050 1055 1060

GAC GAA AGA GAA AGG TAT AAA AAA GAC TTT AAG AAA AGG CTT TTG GAA 144
Asp Glu Arg Glu Arg Tyr Lys Lys Asp Phe Lys Lys Arg Leu Leu Glu
1065 1070 1075

AAG GAA ACA GGA TTC ATA CAG AGA TTA AGA AAA GCG GAA GGA ATA AGG 192
Lys Glu Thr Gly Phe Ile Gln Arg Leu Arg Lys Ala Glu Gly Ile Arg
1080 1085 1090 1095

TGG AGC TTC CAT ACT AGA GAT TAT TAT ATA GGA TAT GTA AGA GAG ATG 240
Trp Ser Phe His Thr Arg Asp Tyr Tyr Ile Gly Tyr Val Arg Glu Met
1100 1105 1110

GTG GCC GGA TCT AGT CTA CCA GAT AGT TTA AGA CTG TAT ATT TAT ATA 288
Val Ala Gly Ser Ser Leu Pro Asp Ser Leu Arg Leu Tyr Ile Tyr Ile
1115 1120 1125

AGC AAT CCA TTG TGG CAC TGG TCA TAC CGT CCT GGC CTG ACA AAT TTT 336
Ser Asn Pro Leu Trp His Trp Ser Tyr Arg Pro Gly Leu Thr Asn Phe
1130 1135 1140

AAT ACA GAA TGG CCT TTT GTG AAT ATG TGG ATA AAG ACA GGA TTC ATG 384
Asn Thr Glu Trp Pro Phe Val Asn Met Trp Ile Lys Thr Gly Phe Met
1145 1150 1155

TGG GAT GAT ATT GAA AGC CAG AAT ATT TGC AAA GGA GGA GAG ATT TCA 432
Trp Asp Asp Ile Glu Ser Gln Asn Ile Cys Lys Gly Gly Glu Ile Ser
1160 1165 1170 1175

CAT GGA TGG GGA CCT GGA ATG GTG GGA ATT GTG ATA AAA GCT TTT AGT 480
His Gly Trp Gly Pro Gly Met Val Gly Ile Val Ile Lys Ala Phe Ser
1180 1185 1190

TGT GGA GAA AGA AAG ATT GAG GCT ACT CCT GTA ATG ATT ATA AGA GGA 528
Cys Gly Glu Arg Lys Ile Glu Ala Thr Pro Val Met Ile Ile Arg Gly
1195 1200 1205

GAA ATA GAT CCA AAA AAA TGG TGT GGA GAT TGT TGG AAT TTG ATG TGT 576
Glu Ile Asp Pro Lys Lys Trp Cys Gly Asp Cys Trp Asn Leu Met Cys
1210 1215 1220

CTT AGG AAC TCA CCT CCA CAG ACT TTA CAA AGA CTT GCT ATG TTG GCA 624
Leu Arg Asn Ser Pro Pro Gln Thr Leu Gln Arg Leu Ala Met Leu Ala
1225 1230 1235

TGT GGC GTG CCG GCT AAG GAG TGG CGA GGA TGC TGT AAT CAA CGC TTT 672
Cys Gly Val Pro Ala Lys Glu Trp Arg Gly Cys Cys Asn Gln Arg Phe
1240 1245 1250 1255

GTT TCT CCT TAC AGA ACG CCT GCT GAT TTG GAG GTC ATT CAA TCC AAG 720
Val Ser Pro Tyr Arg Thr Pro Ala Asp Leu Glu Val Ile Gln Ser Lys

1260 1265 1270

CCC AGC TGG AGT CTA TTA TGG TCA GGG AGC CTA 753
Pro Ser Trp Ser Leu Leu Trp Ser Gly Ser Leu
1275 1280

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 251 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Ile Asp Glu Asp Trp Gln Val Ser Arg Arg Leu Phe Ala Val Leu
1 5 10 15

Gln Gly Gly Val Arg Ser Ala Met Leu Tyr Ile Ser Arg Leu Pro Pro
20 25 30

Asp Glu Arg Glu Arg Tyr Lys Lys Asp Phe Lys Lys Arg Leu Leu Glu
35 40 45

Lys Glu Thr Gly Phe Ile Gln Arg Leu Arg Lys Ala Glu Gly Ile Arg
50 55 60

Trp Ser Phe His Thr Arg Asp Tyr Tyr Ile Gly Tyr Val Arg Glu Met
65 70 75 80

Val Ala Gly Ser Ser Leu Pro Asp Ser Leu Arg Leu Tyr Ile Tyr Ile
85 90 95

Ser Asn Pro Leu Trp His Trp Ser Tyr Arg Pro Gly Leu Thr Asn Phe
100 105 110

Asn Thr Glu Trp Pro Phe Val Asn Met Trp Ile Lys Thr Gly Phe Met
115 120 125

Trp Asp Asp Ile Glu Ser Gln Asn Ile Cys Lys Gly Gly Glu Ile Ser
130 135 140

His Gly Trp Gly Pro Gly Met Val Gly Ile Val Ile Lys Ala Phe Ser
145 150 155 160

Cys Gly Glu Arg Lys Ile Glu Ala Thr Pro Val Met Ile Ile Arg Gly
165 170 175

Glu Ile Asp Pro Lys Lys Trp Cys Gly Asp Cys Trp Asn Leu Met Cys
180 185 190

Leu Arg Asn Ser Pro Pro Gln Thr Leu Gln Arg Leu Ala Met Leu Ala
195 200 205

Cys Gly Val Pro Ala Lys Glu Trp Arg Gly Cys Cys Asn Gln Arg Phe
210 215 220

Val Ser Pro Tyr Arg Thr Pro Ala Asp Leu Glu Val Ile Gln Ser Lys
225 230 235 240

Pro Ser Trp Ser Leu Leu Trp Ser Gly Ser Leu
245 250

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2556 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

ATGGCAGAAG GATTTGCAGC CAATAGACAA TGGATAGGAC CAGAAGAAGC TGAAGAGTTA 60

TTAGATTTTG ATATAGCAAC ACAAATGAAT GAAGAAGGGC CACTAAATCC AGGGATGAAC 120

CCATTTAGGG TACCTGGAAT AACAGATAAA GAAAAGCAAG ACTATTGTAA CATATTACAA 180

CCTAAGTTAC AAGATTTACG GAATGAACTT CAAGAGGTAA AACTAGAAGA AGGAAATGCA 240

GGTAAGTTTA GAAGGGCAAG ATATTTAAGA TATTCTGATG AAAATGTGCT ATCTATAGTC 300

TATTTGCTAA TAGGATATCT AAGATATTTA ATAAATCGTA GGAGTTTAGG ATCTTTAAGA 360

CATGATATAG ACATAGAAAC ACCTCAAGAG GAATATTATA GTAATAGTGA AAGGGGTACC 420

ACATTAAATC AAAAATATGC GAGAAGATGT TGTGTTAGCA CACTTATTAT GTATTTAATT 480

CTTTTTGCAG TAGGCATCTG GTGGGGAGCT AGAGCACAAG TAGTGTGGAG ACTTCCCCCT 540

TTAGTAGTTC CAGTAGAAGA ATCAGAAATA ATTTTTTGGG ATTGTTGGGC ACCAGAAGAA 600

CCCGCCTGTC AAGACTTTCT TGGGGCAATG ATACATCTAA AAGCTAGTAC GAATATAAGT 660

ATACAAGAGG GACCTACCTT GGGGAATTGG GCTAGAGAAA TATGGGGAAC ATTATTCAAA 720

AAGGCTACCA GACAATGTAG AAGAGGTAGA ATATGGAAAA GATGGAATGA AACTATAACA 780

GGACCATTAG GATGTGCTAA TAACACATGT TATAATATTT CAGTAATAGT ACCTGATTAT 840

CAATGTTATC TAGACCGAGT AGATACTTGG TTACAAGGGA AAGTAAATAT ATCATTATGT 900

CTAACAGGAG GAAAAATGTT GTACAATAAA TATACAAAAC AATTAAGCTA TTGTACAGAC 960

CCATTACAAA TCCCACTGAT CAATTATACA TTTGGACCTA ATCAAACATG TATGTGGAAC 1020
ACTTCACAAA TTCAGGACCC TGAGATACCA AAATGTGGAT GGTGGAATCA AAGAGCCTAT 1080
TATAAAAATT GTAAATGGGA AAAAACAGAT GTAAAGTTTC ATTGTCAAAG AACACAGAGT 1140
CAGCCTGGAA CATGGCTTAG AGCAATCTCG TCATGGAGAC AAAGGAATAG ATGGGAATGG 1200
AGACCAGATT TTGAAAGTGA AAAGGTGAAA ATATCTCTAA AGTGTAATAG CACAAAAAAC 1260
CTAACCTTTG CAATGAGAAG TTCAGGAGAT TATGGAGAAG TAACGGGAGC TTGGATAGAG 1320
TTTGGATGTC ATAGAAATAA ATCAAAACTT CATGATGAAG CAAGGTTTAG AATTAGATGT 1380
AGATGGAATA TAGGGGAGAA TACCTCACTC ATTGATACAT GTGGAAACAC TCAAAATGTT 1440
TCAGGGGCAA ATCCTGTAGA TTGTACCATG TATGCAAATA AAATGTACAA TTGTTCTTTA 1500
CAAAACGGGT TTACTATGAA GGTAGATGAC CTTATTATGC ATTTCAATAT GACAAAAGCT 1560
GTAGAAATGT ATAATATTGC TGGAAATTGG TCTTGTACAT CTGACTTGCC ACCAACATGG 1620
GGGTATATGA ATTGTAACTG TACAAATAAT AGTAATGATA ATACTAGAAT GGCATGTCCT 1680
AACAATCAAG GCATCTTAAG GAATTGGTAT AACCCAGTAG CAGGATTACG ACAATCCTTG 1740
GAAAAGTATC AAGTTGTAAA ACAACCAGAT TACTTAGTGG TCCCAGGGGA AGTCATGGAA 1800
TATAAAACTA GAAGGAAAAG GGCAGCTATT CATGTTATGT TAGCTCTTGC AACAGTATTA 1860
TCTATGGCCG GAGCAGGGAC GGGGGCTACT GCTATAGGGA TGGTAACACA ATATCACCAA 1920
GTTCTAGCAA CCCATCAAGA AGCTATTGAA AAGGTGACTG AAGCCTTAAA GATAAACAAC 1980
TTGAGATTAG TTACATTAGA GCATCAAGTA CTAGTAATAG GATTAAAAGT AGAAGCTATG 2040
GAAAAATTTT TATATACAGC TTTCGCTATG CAAGAATTAG GATGTAATCA AAATCAATTC 2100
TTCTGCAAAG TCCCTCCTGA ATTGTGGATG AGGTATAATA TGTCTATAAA TCAAACAATA 2160
TGGAATCATG GAAATATAAC TTTGGGGGAA TGGTATAACC AAACAAAAGA TTTACAACAA 2220
AAGTTTTATG AAATAATAAT GGACATAGAA CAAAATAATG TACAAGGGAA AAAAGGGATA 2280
CAACAATTAC AAAAGTGGGA AGATTGGGTA GGATGGATAG GAAATATTCC ACAATACTTA 2340
AAGGGACTAT TGGGAGGTAT CTTGGGAATA GGATTAGGAG TGTTATTATT AATTTTATGT 2400
TTACCCACAT TGGTTGATTG TATAAGAAAT TGTATCCACA AGATACTAGG ATACACAGTA 2460
ATTGCAATGC CTGAAGTAGA AGGAGAAGAA ATACAACCAC AAATGGAATT GAGGAGAAAT 2520
GGTAGGCAAT GTGGCATATC TGAAAAAGAG GAGGAA 2556

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..36

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
CAA GAA TTA GGA TGT AAT CAA AAT CAA TTC TTC TGC                36
Gln Glu Leu Gly Cys Asn Gln Asn Gln Phe Phe Cys
            255                 260
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Gln Glu Leu Gly Cys Asn Gln Asn Gln Phe Phe Cys
  1               5                  10
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GGATGAGTAT TGGAACCCTG AA 22

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GATTCCGAGA CCTCACAGGT AA 22

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

AATAGGGAAG CAGTAGCAGA C 21

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GTAAATCGCA AATAACCAAC C 21

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

TGACGGTGTC TACTGCTGCT 20

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CACACTGGTC CTGATCCTTT T 21

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CCACAATATG TAGCACTTGA CC 22

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGGTACTTTC TGGCTTAAGG TG 22

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GGGGGACCTA CCTTGGGGAA TTGGGCT 27

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GGTGATCATG ATCAGTGGGA TTTGTAATGG GTCTG 35

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GGTGATCATG ATCAGTGGGA TTTGTAATGG GTCTG 35

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

ATAAGGGAGA TACTGTGCTG A 21

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GCGATCTTCT AACTCTGTCA T 21

THAT WHICH IS CLAIMED IS:

1. An isolated feline immunodeficiency virus (FIV) having all of the identifying characteristics of FIV clone JSY3.

2. An isolated feline immunodeficiency virus (FIV) whose proviral DNA comprises a DNA sequence selected from the group consisting of SEQ ID NO:1 and sequences which vary from SEQ ID NO:1 due to the degeneracy of the genetic code.

3. A biologically pure culture of host cells containing the feline immunodeficiency virus of claim 1.

4. A biologically pure culture of host cells containing the feline immunodeficiency virus of claim 2.

5. Isolated DNA comprising a DNA sequence selected from the group consisting of SEQ ID NO:1 and sequences which vary from SEQ ID NO:1 due to the degeneracy of the genetic code.

6. A vector comprising DNA of claim 5.

7. A vector according to claim 6, wherein said vector comprises bacteriophage lambda.

8. A host cell containing and capable of expressing a vector according to claim 6.

9. A host cell according to claim 8, wherein said host cell comprises *Escherichia coli*.

10. A host cell according to claim 8, wherein said host cell comprises a yeast cell.

11. A host cell according to claim 8, wherein said host cell comprises a mammalian host cell.

12. Isolated DNA comprising a DNA sequence selected from the group consisting of:

(a) SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:19; and

(b) sequences which vary from those of (a) above due to the degeneracy of the genetic code.

13. A vector comprising DNA of claim 12.

14. A vector according to claim 13, wherein said vector comprises bacteriophage lambda.

15. A host cell containing and capable of expressing a vector according to claim 13.

16. A host cell according to claim 15, wherein said host cell comprises *Escherichia coli*.

17. A host cell according to claim 15, wherein said host cell comprises a yeast cell.

18. A host cell according to claim 15, wherein said host cell comprises a mammalian host cell.

19. A polypeptide having a sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:15, SEO ID NO:17, and SEQ ID NO:20.

20. A specific pathogen free (SPF) cat infected with feline immunodeficiency virus clone JSY3.

21. A colony of SPF cats according to claim 20.

FIGURE 1

```
         430       440       450       460       470       480
       *   *     *   *     *   *     *   *     *   *     *   *
TTCTGGGATG AGTATTGGGA CCCTGAAGAA ATAGAAAGAA TGCTTATGGA CTAGTGACTG
AAGACCCTAC TCATAACCCT GGGACTTCTT TATCTTTCTT ACGAATACCT GATCACTGAC
  → JSY3

         490       500       510       520       530       540
       *   *     *   *     *   *     *   *     *   *     *   *
TTTACGAACA AATGATAAAT GATGGAAACA GCTGAGCATG ACTCATAGTT AAAGCGCTAG
AAATGCTTGT TTACTATTTA CTACCTTTGT CGACTCGTAC TGAGTATCAA TTTCGCGATC

         550       560       570       580       590       600
       *   *     *   *     *   *     *   *     *   *     *   *
CAGCTGCTTA ACCGCAAAAC CACATCCTAT GTAAAGCTTG CTGATGACGT ATAATTTGCT
GTCGACGAAT TGGCGTTTTG GTGTAGGATA CATTTCGAAC GACTACTGCA TATTAAACGA

         610       620       630       640       650       660
       *   *     *   *     *   *     *   *     *   *     *   *
CCACTGTAAA AGTATATAAC CAGTGCTTTG TGAGACTTCG GGGAGTCTCT CCGTTGAGGA
GGTGACATTT TCATATATTG GTCACGAAAC ACTCTGAAGC CCCTCAGAGA GGCAACTCCT

         670       680       690       700       710       720
       *   *     *   *     *   *     *   *     *   *     *   *
CTTTCGAGTT CTCCCTTGAG GCTCCCACAG ATACAATAAA TATTTGAGAT TGAACCCTGT
GAAAGCTCAA GAGGGAACTC CGAGGGTGTC TATGTTATTT ATAAACTCTA ACTTGGGACA

         730       740       750       760       770       780
       *   *     *   *     *   *     *   *     *   *     *   *
CAAGTATCTG TGTAATCTTT TTTACCTGTG AGGTCTCGGA ATCCGGGCCG AGAACTTCGC
GTTCATAGAC ACATTAGAAA AAATGGACAC TCCAGAGCCT TAGGCCCGGC TCTTGAAGCG

         790       800       810       820       830       840
       *   *     *   *     *   *     *   *     *   *     *   *
AGTTGGCGCC CGAACAGGGA CTTGATTGAG AGTGATTGAG GAAGTGAAGC TAGAGCAATA
TCAACCGCGG GCTTGTCCCT GAACTAACTC TCACTAACTC CTTCACTTCG ATCTCGTTAG

         850       860       870       880       890       900
       *   *     *   *     *   *     *   *     *   *     *   *
GAAAGCTGTT AAGCAGAACT CCTGCTGACC TAAATAGGGA AGCAGTAGCA GACGCTGCTA
CTTTCGACAA TTCGTCTTGA GGACGACTGG ATTTATCCCT TCGTCATCGT CTGCGACGAT
```

Figure 1, continued

```
       910        920        930        940        950        960
         *    *     *    *     *    *     *    *     *    *     *    *
ACAGTGAGTA TCTCTAGTGA AGCAGACTCG AGCTCATAAT CAAGTCACTG TTTAAAGGCC
TGTCACTCAT AGAGATCACT TCGTCTGAGC TCGAGTATTA GTTCAGTGAC AAATTTCCGG

       970        980        990       1000       1010       1020
         *    *     *    *     *    *     *    *     *    *     *    *
CAGATAAATT ACATCTGGTG ACTCTTCGCG GACCTTCAAG CCAGGAGATT CGCCGAGGGA
GTCTATTTAA TGTAGACCAC TGAGAAGCGC CTGGAAGTTC GGTCCTCTAA GCGGCTCCCT

      1030       1040       1050       1060       1070       1080
         *    *     *    *     *    *     *    *     *    *     *    *
CAGTCAACAA GGTAGGAGAG ATTCTGCAGC AACATGGGGA ACGGACAGGG GCGAGATTGG
GTCAGTTGTT CCATCCTCTC TAAGACGTCG TTGTACCCCT TGCCTGTCCC CGCTCTAACC
                                    M  G   N  G  Q  G   R  D  W>
                            GAG →

      1090       1100       1110       1120       1130       1140
         *    *     *    *     *    *     *    *     *    *     *    *
AAAATGGCCA TTAAGAGATG TAGTAATGTT GCTGTAGGAG TAGGGGGGAA GAGTAAAAAA
TTTTACCGGT AATTCTCTAC ATCATTACAA CGACATCCTC ATCCCCCCTT CTCATTTTTT
 K  M  A   I  K  R  C   S  N  V   A  V  G   V  G  G  K   S  K  K>

      1150       1160       1170       1180       1190       1200
         *    *     *    *     *    *     *    *     *    *     *    *
TTTGGAGAAG GGAATTTCAG ATGGGCCATT AGAATGGCTA ATGTATCTAC AGGACGAGAA
AAACCTCTTC CCTTAAAGTC TACCCGGTAA TCTTACCGAT TACATAGATG TCCTGCTCTT
 F  G  E   G  N  F  R   W  A  I   R  M  A   N  V  S  T   G  R  E>

      1210       1220       1230       1240       1250       1260
         *    *     *    *     *    *     *    *     *    *     *    *
CCTGGTGATA TACCAGAGAC TTTAGATCAA CTAAGGTTGG TTATTTGCGA TTTACAAGAA
GGACCACTAT ATGGTCTCTG AAATCTAGTT GATTCCAACC AATAAACGCT AAATGTTCTT
 P  G  D   I  P  E  T   L  D  Q   L  R  L   V  I  C  D   L  Q  E>

      1270       1280       1290       1300       1310       1320
         *    *     *    *     *    *     *    *     *    *     *    *
AGAAGAGAAA AATTTGGGTC GAGCAAAGAA ATTGACATGG CAATTGTTAC ATTAAAAGTC
TCTTCTCTTT TTAAACCCAG CTCGTTTCTT TAACTGTACC GTTAACAATG TAATTTTCAG
 R  R  E   K  F  G  S   S  K  E   I  D  M   A  I  V  T   L  K  V>

      1330       1340       1350       1360       1370       1380
         *    *     *    *     *    *     *    *     *    *     *    *
TTTGCGGTAG TAGGACTTTT AAATATGACA GTGTCTACTG CTGCTGCAGC TGAAAATATG
AAACGCCATC ATCCTGAAAA TTTATACTGT CACAGATGAC GACGACGTCG ACTTTTATAC
 F  A  V   V  G  L  L   N  M  T   V  S  T   A  A  A  A   E  N  M>
```

3/44

Figure 1, continued

```
      1390      1400      1410      1420      1430      1440
         *         *         *         *         *         *
TACACTCAGA TGGGATTAGA CACTAGACCA TCTATGAGAG AAGCAGGAGG AAAAGAGGAA
ATGTGAGTCT ACCCTAATCT GTGATCTGGT AGATACTCTC TTCGTCCTCC TTTTCTCCTT
 Y  T  Q   M  G  L  D   T  R  P   S  M  R   E  A  G  G   K  E  E>

      1450      1460      1470      1480      1490      1500
         *         *         *         *         *         *
AGCCCTCCAC AGGCATCTCC TATTCAAACA GCAAATGGAG CACCACAATA TGTAGCACTT
TCGGGAGGTG TCCGTAGAGG ATAAGTTTGT CGTTTACCTC GTGGTGTTAT ACATCGTGAA
 S  P  P   Q  A  S  P   I  Q  T   A  N  G   A  P  Q  Y   V  A  L>
          p15  ←  →  p25

      1510      1520      1530      1540      1550      1560
         *         *         *         *         *         *
GACCCAAAAA TGGTGTCCAT TTTTATGGAA AAGGCAAGAG AAGGATTAGG AGGTGAGGAA
CTGGGTTTTT ACCACAGGTA AAAATACCTT TTCCGTTCTC TTCCTAATCC TCCACTCCTT
 D  P  K   M  V  S  I   F  M  E   K  A  R   E  G  L  G   G  E  E>

      1570      1580      1590      1600      1610      1620
         *         *         *         *         *         *
GTTCAGCTAT GGTTTACTGC CTTCTCTGCA AATTTAACAC CTACTGACAT GGCCACATTA
CAAGTCGATA CCAAATGACG GAAGAGACGT TTAAATTGTG GATGACTGTA CCGGTGTAAT
 V  Q  L   W  F  T  A   F  S  A   N  L  T   P  T  D  M   A  T  L>

      1630      1640      1650      1660      1670      1680
         *         *         *         *         *         *
ATAATGGCCG CACCAGGGTG CGCTGCAGAT AAAGAAATAT TGGATGAAAG CTTAAAGCAA
TATTACCGGC GTGGTCCCAC GCGACGTCTA TTTCTTTATA ACCTACTTTC GAATTTCGTT
 I  M  A   A  P  G  C   A  A  D   K  E  I   L  D  E  S   L  K  Q>

      1690      1700      1710      1720      1730      1740
         *         *         *         *         *         *
TTGACGGCAG AGTATGATCG TACCCATCCT CCTGATGGAC CTAGACCATT ACCCTATTTT
AACTGCCGTC TCATACTAGC ATGGGTAGGA GGACTACCTG GATCTGGTAA TGGGATAAAA
 L  T  A   E  Y  D  R   T  H  P   P  D  G   P  R  P   L   P  Y  F>
       ______________________________________________
                           p24A

      1750      1760      1770      1780      1790      1800
         *         *         *         *         *         *
ACTGCAGCAG AAATTATGGG TATAGGATTA ACTCAAGAAC AACAAGCAGA AGCAAGATTT
TGACGTCGTC TTTAATACCC ATATCCTAAT TGAGTTCTTG TTGTTCGTCT TCGTTCTAAA
 T  A  A   E  I  M  G   I  G  L   T  Q  E   Q  Q  A  E   A  R  F>
```

Figure 1, continued

```
      1810       1820       1830       1840       1850       1860
        *    *     *    *     *    *     *    *     *    *     *    *
GCACCAGCTA GGATGCAGTG TAGAGCATGG TATCTCGAGG CACTAGGAAA ATTGGCCGCC
CGTGGTCGAT CCTACGTCAC ATCTCGTACC ATAGAGCTCC GTGATCCTTT TAACCGGCGG
 A  P  A   R  M  Q  C   R  A  W   Y  L  E   A  L  G  K   L  A  A>

      1870       1880       1890       1900       1910       1920
        *    *     *    *     *    *     *    *     *    *     *    *
ATAAAAGCTA AGTCTCCTCG AGCTGTGCAG TTAAGACAAG GAGCTAAGGA AGATTATTCA
TATTTTCGAT TCAGAGGAGC TCGACACGTC AATTCTGTTC CTCGATTCCT TCTAATAAGT
 I  K  A   K  S  P  R   A  V  Q   L  R  Q   G  A  K  E   D  Y  S>

      1930       1940       1950       1960       1970       1980
        *    *     *    *     *    *     *    *     *    *     *    *
TCCTTTATAG ACAGATTGTT TGCCCAAATA GATCAAGAAC AAAATACAGC TGAAGTTAAG
AGGAAATATC TGTCTAACAA ACGGGTTTAT CTAGTTCTTG TTTTATGTCG ACTTCAATTC
 S  F  I   D  R  L  F   A  Q  I   D  Q  E   Q  N  T  A   E  V  K>

      1990       2000       2010       2020       2030       2040
        *    *     *    *     *    *     *    *     *    *     *    *
TTATATTTAA AACAGTCATT AAGCATGGCT AATGCTAATG CAGAATGTAA AAAGGCAATG
AATATAAATT TTGTCAGTAA TTCGTACCGA TTACGATTAC GTCTTACATT TTTCCGTTAC
 L  Y  L   K  Q  S  L   S  M  A   N  A  N   A  E  C  K   K  A  M>

      2050       2060       2070       2080       2090       2100
        *    *     *    *     *    *     *    *     *    *     *    *
AGCCACCTTA AGCCAGAAAG TACCCTAGAA GAAAAGCTGA GAGCTTGTCA AGAAGTAGGC
TCGGTGGAAT TCGGTCTTTC ATGGGATCTT CTTTTCGACT CTCGAACAGT TCTTCATCCG
 S  H  L   K  P  E  S   T  L  E   E  K  L   R  A  C  Q   E  V  G>

      2110       2120       2130       2140       2150       2160
        *    *     *    *     *    *     *    *     *    *     *    *
TCACCAGGAT ATAAAATGCA ACTCTTGGCA GAAGCTCTTA CAAAAGTTCA AGTAGTGCAA
AGTGGTCCTA TATTTTACGT TGAGAACCGT CTTCGAGAAT GTTTTCAAGT TCATCACGTT
 S  P  G   Y  K  M  Q   L  L  A   E  A  L   T  K  V  Q   V  V  Q>
                      p25  ←              →  p10

      2170       2180       2190       2200       2210       2220
        *    *     *    *     *    *     *    *     *    *     *    *
TCAAAAGGAT CAGGACCAGT GTGTTTCAAC TGTAAAAAAC CAGGACATCT AGCAAAACAG
AGTTTTCCTA GTCCTGGTCA CACAAAGTTG ACATTTTTTG GTCCTGTAGA TCGTTTTGTC
 S  K  G   S  G  P  V   C  F  N   C  K  K   P  G  H  L   A  K  Q>

      2230       2240       2250       2260       2270       2280
        *    *     *    *     *    *     *    *     *    *     *    *
TGTAGAGATG TGAAAAAATG TAATAAATGT GGAAAGCCTG GTCATTTAGC TGCCAAATGC
ACATCTCTAC ACTTTTTTAC ATTATTTACA CCTTTCGGAC CAGTAAATCG ACGGTTTACG
```

Figure 1, continued

```
C  R  D   V  K  K  C   N  K  C   G  K  P   G  H  L  A   A  K  C>

      2290       2300       2310       2320       2330       2340
     *    *     *    *     *    *     *    *     *    *     *    *
TGGCAAGGTG GTAAAAAGAA TTCGGGAAAC TGGAAGGCGG GGCGAGCTGC AGCCCCAGTG
ACCGTTCCAC CATTTTTCTT AAGCCCTTTG ACCTTCCGCC CCGCTCGACG TCGGGGTCAC
 W  Q  G   G  K  K  N   S  G  N   W  K  A   G  R  A  A   A  P  V>

      2350       2360       2370       2380       2390       2400
     *    *     *    *     *    *     *    *     *    *     *    *
AATCAAGTGC AGCAAGCAGT AATGCCATCT GCACCTCCAA TGGAGGAGAG ACTATTGGAT
TTAGTTCACG TCGTTCGTCA TTACGGTAGA CGTGGAGGTT ACCTCCTCTC TGATAACCTA
 N  Q  V   Q  Q  A  V   M  P  S   A  P  P   M  E  E  R   L  L  D>

      2410       2420       2430       2440       2450       2460
     *    *     *    *     *    *     *    *     *    *     *    *
TTATAAATTA TAATAAAGTA GGTACTACTA CAACATTAGA AAAGAGGCCA GAAATACTTA
AATATTTAAT ATTATTTCAT CCATGATGAT GTTGTAATCT TTTCTCCGGT CTTTATGAAT
 L>
 ← p10

      2470       2480       2490       2500       2510       2520
     *    *     *    *     *    *     *    *     *    *     *    *
TATTTGTAAA TGGGTACCCT ATAAAATTTT TATTAGATAC AGGAGCAGAT ATAACAATTT
ATAAACATTT ACCCATGGGA TATTTTAAAA ATAATCTATG TCCTCGTCTA TATTGTTAAA

      2530       2540       2550       2560       2570       2580
     *    *     *    *     *    *     *    *     *    *     *    *
TAAATAGGAG AGATTTTCAA GTAAAAAATT CTATAGAAAA TGGAAGGCAA AATATGATTG
ATTTATCCTC TCTAAAAGTT CATTTTTTAA GATATCTTTT ACCTTCCGTT TTATACTAAC
                                                         M  I>
                                                       → pol
                                                         ORF1

      2590       2600       2610       2620       2630       2640
     *    *     *    *     *    *     *    *     *    *     *    *
GAGTAGGAGG AGGAAAGAGA GGAACAAATT ATATCAATGT GCATTTAGAG ATTAGAGATG
CTCATCCTCC TCCTTTCTCT CCTTGTTTAA TATAGTTACA CGTAAATCTC TAATCTCTAC
 G  V  G  G   G  K  R   G  T  N   Y  I  N  V   H  L  E   I  R  D>

      2650       2660       2670       2680       2690       2700
     *    *     *    *     *    *     *    *     *    *     *    *
AAAATTATAA GACACAATGT ATATTTGGCA ATGTTTGTGT CTTAGAAGAT AACTCATTAA
TTTTAATATT CTGTGTTACA TATAAACCGT TACAAACACA GAATCTTCTA TTGAGTAATT
 E  N  Y  K   T  Q  C   I  F  G   N  V  C  V   L  E  D   N  S  L>
```

Figure 1, continued

```
      2710      2720      2730      2740      2750      2760
       *    *    *    *    *    *    *    *    *    *    *    *
TACAACCATT ATTAGGGAGA GATAATATGA TTAGATTCAA TATTAGGTTA GTAATGGCTC
ATGTTGGTAA TAATCCCTCT CTATTATACT AATCTAAGTT ATAATCCAAT CATTACCGAG
I  Q  P  L   L  G  R   D  N  M   I  R  F  N   I  R  L   V  M  A>

      2770      2780      2790      2800      2810      2820
       *    *    *    *    *    *    *    *    *    *    *    *
AAATTTCTGA CAAGATTCCA ATAGTAAAAG TAAAAATGAA GGATCCAAAT AAAGGACCTC
TTTAAAGACT GTTCTAAGGT TATCATTTTC ATTTTTACTT CCTAGGTTTA TTTCCTGGAG
Q  I  S  D   K  I  P   I  V  K   V  K  M  K   D  P  N   K  G  P>

      2830      2840      2850      2860      2870      2880
       *    *    *    *    *    *    *    *    *    *    *    *
AAATAAAACA ATGGCCATTA ACAAATGAAA AAATTGAAGC TTTAACAGAA ATAGTAGAAA
TTTATTTTGT TACCGGTAAT TGTTTACTTT TTTAACTTCG AAATTGTCTT TATCATCTTT
Q  I  K  Q   W  P  L   T  N  E   K  I  E  A   L  T  E   I  V  E>

      2890      2900      2910      2920      2930      2940
       *    *    *    *    *    *    *    *    *    *    *    *
GACTAGAAAG AGAAGGGAAA GTAAAAAGAG CAGATCCAAA TAACCCATGG AATACACCAG
CTGATCTTTC TCTTCCCTTT CATTTTTCTC GTCTAGGTTT ATTGGGTACC TTATGTGGTC
R  L  E  R   E  G  K   V  K  R   A  D  P  N   N  P  W   N  T  P>

      2950      2960      2970      2980      2990      3000
       *    *    *    *    *    *    *    *    *    *    *    *
TATTTGCAAT AAAAAAGAAA AGTGGAAAAT GGAGAATGCT CATAGATTTT AGAGAATTGA
ATAAACGTTA TTTTTTCTTT TCACCTTTTA CCTCTTACGA GTATCTAAAA TCTCTTAACT
V  F  A  I   K  K  K   S  G  K   W  R  M  L   I  D  F   R  E  L>

      3010      3020      3030      3040      3050      3060
       *    *    *    *    *    *    *    *    *    *    *    *
ACAAATTAAC TGAGAAAGGG GCAGAAGTCC AGTTAGGACT CCCTCATCCT GCTGGATTAA
TGTTTAATTG ACTCTTTCCC CGTCTTCAGG TCAATCCTGA GGGAGTAGGA CGACCTAATT
N  K  L  T   E  K  G   A  E  V   Q  L  G  L   P  H  P   A  G  L>

      3070      3080      3090      3100      3110      3120
       *    *    *    *    *    *    *    *    *    *    *    *
AAATGAAAAA ACAAGTTACT GTGCTAGATA TAGGAGATGC ATACTTCACT ATTCCCTTGG
TTTACTTTTT TGTTCAATGA CACGATCTAT ATCCTCTACG TATGAAGTGA TAAGGGAACC
K  M  K  K   Q  V  T   V  L  D   I  G  D  A   Y  F  T   I  P  L>

      3130      3140      3150      3160      3170      3180
       *    *    *    *    *    *    *    *    *    *    *    *
ATCCAGACTA TGCTCCCTAT ACTGCATTCA CATTACCTAG AAAGAATAAT GCAGGACCAG
TAGGTCTGAT ACGAGGGATA TGACGTAAGT GTAATGGATC TTTCTTATTA CGTCCTGGTC
D  P  D  Y   A  P  Y   T  A  F   T  L  P  R   K  N  N   A  G  P>
```

Figure 1, continued

```
         3190      3200      3210      3220      3230      3240
           *    *    *    *    *    *    *    *    *    *    *    *
GGAGGAGATA TGTATGGTGC AGTTTACCAC AGGGGTGGGT TCTAAGCCCA TTGATATATC
CCTCCTCTAT ACATACCACG TCAAATGGTG TCCCCACCCA AGATTCGGGT AACTATATAG
G  R  R  Y   V  W  C   S  L  P   Q  G  W  V   L  S  P   L  I  Y>

         3250      3260      3270      3280      3290      3300
           *    *    *    *    *    *    *    *    *    *    *    *
AAAGTACTTT AGATAATATA ATACAACCTT TTATTAGACA AAATCCTGAG TTAGATATTT
TTTCATGAAA TCTATTATAT TATGTTGGAA AATAATCTGT TTTAGGACTC AATCTATAAA
Q  S  T  L   D  N  I   I  Q  P   F  I  R  Q   N  P  E   L  D  I>

         3310      3320      3330      3340      3350      3360
           *    *    *    *    *    *    *    *    *    *    *    *
ATCAATATAT GGATGACATT TATATAGGAT CAAACTTAAG TAAAAAGGAG CATAAAGAAA
TAGTTATATA CCTACTGTAA ATATATCCTA GTTTGAATTC ATTTTTCCTC GTATTTCTTT
Y  Q  Y  M   D  D  I   Y  I  G   S  N  L  S   K  K  E   H  K  E>

         3370      3380      3390      3400      3410      3420
           *    *    *    *    *    *    *    *    *    *    *    *
AAGTAGAAGA ATTAAGAAAA TTGTTATTAT GGTGGGGATT TGAAACCCCG GAAGACAAAT
TTCATCTTCT TAATTCTTTT AACAATAATA CCACCCCTAA ACTTTGGGGC CTTCTGTTTA
K  V  E  E   L  R  K   L  L  L   W  W  G  F   E  T  P   E  D  K>

         3430      3440      3450      3460      3470      3480
           *    *    *    *    *    *    *    *    *    *    *    *
TACAAGAAGA GCCCCCATAT AAGTGGATGG GCTATGAATT ACATCCATTA ACATGGTCAA
ATGTTCTTCT CGGGGGTATA TTCACCTACC CGATACTTAA TGTAGGTAAT TGTACCAGTT
L  Q  E  E   P  P  Y   K  W  M   G  Y  E  L   H  P  L   T  W  S>

         3490      3500      3510      3520      3530      3540
           *    *    *    *    *    *    *    *    *    *    *    *
TACAGCAAAA ACAATTAGAA ATTCCAGAAA GACCCACATT AAATGAACTG CAGAAATTAG
ATGTCGTTTT TGTTAATCTT TAAGGTCTTT CTGGGTGTAA TTTACTTGAC GTCTTTAATC
I  Q  Q  K   Q  L  E   I  P  E   R  P  T  L   N  E  L   Q  K  L>

         3550      3560      3570      3580      3590      3600
           *    *    *    *    *    *    *    *    *    *    *    *
CAGGTAAGAT AAACTGGGCC AGTCAAACTA TCCCAGACTT AAGTATAAAA GAACTAACTA
GTCCATTCTA TTTGACCCGG TCAGTTTGAT AGGGTCTGAA TTCATATTTT CTTGATTGAT
A  G  K  I   N  W  A   S  Q  T   I  P  D  L   S  I  K   E  L  T>

         3610      3620      3630      3640      3650      3660
           *    *    *    *    *    *    *    *    *    *    *    *
ACATGATGAG AGGAGATCAG AAGTTAGACT CAATAAGAGA ATGGACTGTG GAAGCCAAGA
TGTACTACTC TCCTCTAGTC TTCAATCTGA GTTATTCTCT TACCTGACAC CTTCGGTTCT
N  M  M  R   G  D  Q   K  L  D   S  I  R  E   W  T  V   E  A  K>
```

Figure 1, continued

```
       3670      3680      3690      3700      3710      3720
          *         *         *         *         *         *
GAGAAGTACA AAAAGCTAAG GAAGCTATTG AGATGCAAGC ACAGCTAAAT TATTATGATC
CTCTTCATGT TTTTCGATTC CTTCGATAAC TCTACGTTCG TGTCGATTTA ATAATACTAG
R  E  V  Q   K  A  K   E  A  I   E  M  Q  A   Q  L  N   Y  Y  D>

       3730      3740      3750      3760      3770      3780
          *         *         *         *         *         *
CCCACCGAGA ATTATATGCA AAATTAAGTT TAGTGGGACC ACATCAAATA TGTTATCAAG
GGGTGGCTCT TAATATACGT TTTAATTCAA ATCACCCTGG TGTAGTTTAT ACAATAGTTC
P  H  R  E   L  Y  A   K  L  S   L  V  G  P   H  Q  I   C  Y  Q>

       3790      3800      3810      3820      3830      3840
          *         *         *         *         *         *
TGTATCATAA GAACCCAGAA TGTATTTTAT GGTATGGTAA GATGAATAGA CAAAAGAAAA
ACATAGTATT CTTGGGTCTT ACATAAAATA CCATACCATT CTACTTATCT GTTTTCTTTT
V  Y  H  K   N  P  E   C  I  L   W  Y  G  K   M  N  R   Q  K  K>

       3850      3860      3870      3880      3890      3900
          *         *         *         *         *         *
AGGCAGAAAA TACCTGTGAT ATAGCTCTAA GGGCATGTTA TAAAATAAGA GAAGAATCTA
TCCGTCTTTT ATGGACACTA TATCGAGATT CCCGTACAAT ATTTTATTCT CTTCTTAGAT
K  A  E  N   T  C  D   I  A  L   R  A  C  Y   K  I  R   E  E  S>

       3910      3920      3930      3940      3950      3960
          *         *         *         *         *         *
TTATAAGAAT AGGAAAAGAA CCAATATATG AAATACCTAC TTCTAGAGAA GCCTGGGAGT
AATATTCTTA TCCTTTTCTT GGTTATATAC TTTATGGATG AAGATCTCTT CGGACCCTCA
I  I  R  I   G  K  E   P  I  Y   E  I  P  T   S  R  E   A  W  E>

       3970      3980      3990      4000      4010      4020
          *         *         *         *         *         *
CAAATTTAAT TAATTCACCA TATCTTAAGG CCCCACCTCC TGAGGTAGAA TATATCCATG
GTTTAAATTA ATTAAGTGGT ATAGAATTCC GGGGTGGAGG ACTCCATCTT ATATAGGTAC
S  N  L  I   N  S  P   Y  L  K   A  P  P  P   E  V  E   Y  I  H>

       4030      4040      4050      4060      4070      4080
          *         *         *         *         *         *
CTGCTGTGAA TATAAAAAGA GCATTAAGTA TGATAAAAGA TGTTCCAATA CCAGAAGCAG
GACGACACTT ATATTTTTCT CGTAATTCAT ACTATTTTCT ACAAGGTTAT GGTCTTCGTC
A  A  V  N   I  K  R   A  L  S   M  I  K  D   V  P  I   P  E  A>

       4090      4100      4110      4120      4130      4140
          *         *         *         *         *         *
AAACGTGGTA TATAGATGGA GGCAGAAAGC TAGGAAAAGC AGCAAAAGCA GCCTATTGGA
TTTGCACCAT ATATCTACCT CCGTCTTTCG ATCCTTTTCG TCGTTTTCGT CGGATAACCT
E  T  W  Y   I  D  G   G  R  K   L  G  K  A   A  K  A   A  Y  W>
```

Figure 1, continued

```
    4150      4160      4170      4180      4190      4200
       *         *         *         *         *         *
CAGATACAGG GAAGTGGCAA GTAATGGAGT TAGAAGGCAG TAATCAGAAG GCAGAAGTAC
GTCTATGTCC CTTCACCGTT CATTACCTCA ATCTTCCGTC ATTAGTCTTC CGTCTTCATG
T  D  T  G   K  W  Q   V  M  E   L  E  G  S   N  Q  K   A  E  V>

    4210      4220      4230      4240      4250      4260
       *         *         *         *         *         *
AAGCATTATT ATTGGCATTA AAAGCAGGAT CAGAGGAAAT GAATATTATA ACAGATTCAC
TTCGTAATAA TAACCGTAAT TTTCGTCCTA GTCTCCTTTA CTTATAATAT TGTCTAAGTG
Q  A  L  L   L  A  L   K  A  G   S  E  E  M   N  I  I   T  D  S>

    4270      4280      4290      4300      4310      4320
       *         *         *         *         *         *
AATATGTTAT AAATATTATT CTTCAACAAC CAGATATGAT GGAGGGAATC TGGCAAGAAG
TTATACAATA TTTATAATAA GAAGTTGTTG GTCTATACTA CCTCCCTTAG ACCGTTCTTC
Q  Y  V  I   N  I  I   L  Q  Q   P  D  M  M   E  G  I   W  Q  E>

    4330      4340      4350      4360      4370      4380
       *         *         *         *         *         *
TTTTAGAAGA ATTGGAGAAA AAAACAGCAA TATTTATAGA TTGGGTCCCA GGACATAAAG
AAAATCTTCT TAACCTCTTT TTTTGTCGTT ATAAATATCT AACCCAGGGT CCTGTATTTC
V  L  E  E   L  E  K   K  T  A   I  F  I  D   W  V  P   G  H  K>

    4390      4400      4410      4420      4430      4440
       *         *         *         *         *         *
GTATTCCAGG AAATGAGGAA GTAGATAAGC TTTGTCAAAC AATGATGATA ATAGAAGGGG
CATAAGGTCC TTTACTCCTT CATCTATTCG AAACAGTTTG TTACTACTAT TATCTTCCCC
G  I  P  G   N  E  E   V  D  K   L  C  Q  T   M  M  I   I  E  G>

    4450      4460      4470      4480      4490      4500
       *         *         *         *         *         *
ATGGGATATT AGATAAAAGG TCAGAAGATG CGGGATATGA TTTATTGGCT GCAAAAGAAA
TACCCTATAA TCTATTTTCC AGTCTTCTAC GCCCTATACT AAATAACCGA CGTTTTCTTT
D  G  I  L   D  K  R   S  E  D   A  G  Y  D   L  L  A   A  K  E>

    4510      4520      4530      4540      4550      4560
       *         *         *         *         *         *
TACATTTATT GCCAGGAGAG GTAAAAGTAA TACCAACAGG GGTAAAGCTA ATGCTGCCTA
ATGTAAATAA CGGTCCTCTC CATTTTCATT ATGGTTGTCC CCATTTCGAT TACGACGGAT
I  H  L  L   P  G  E   V  K  V   I  P  T  G   V  K  L   M  L  P>

    4570      4580      4590      4600      4610      4620
       *         *         *         *         *         *
AAGGACATTG GGGACTAATA ATGGGAAGAA GCTCGATAGG GAGTAAAGGA TTGGATGTAT
TTCCTGTAAC CCCTGATTAT TACCCTTCTT CGAGCTATCC CTCATTTCCT AACCTACATA
K  G  H  W   G  L  I   M  G  R   S  S  I  G   S  K  G   L  D  V>
```

Figure 1, continued

```
     4630      4640      4650      4660      4670      4680
   *    *    *    *    *    *    *    *    *    *    *    *
TAGGAGGGGT AATAGATGAA GGATATCGAG GTGAAATTGG AGTAATAATG ATTAATGTAT
ATCCTCCCCA TTATCTACTT CCTATAGCTC CACTTTAACC TCATTATTAC TAATTACATA
L  G  G  V   I  D  E   G  Y  R   G  E  I  G   V  I  M   I  N  V>

     4690      4700      4710      4720      4730      4740
   *    *    *    *    *    *    *    *    *    *    *    *
CAAGAAAATC AATCACCTTA ATGGAACAAC AAAAGATAGC ACAATTAATA ATATTGCCTT
GTTCTTTTAG TTAGTGGAAT TACCTTGTTG TTTTCTATCG TGTTAATTAT TATAACGGAA
S  R  K  S   I  T  L   M  E  Q   Q  K  I  A   Q  L  I   I  L  P>

     4750      4760      4770      4780      4790      4800
   *    *    *    *    *    *    *    *    *    *    *    *
GTAAACATGA AGTATTAGAA CAAGGAAAAG TTGTAATGGA TTCAGAGAGA GGAGACAAAG
CATTTGTACT TCATAATCTT GTTCCTTTTC AACATTACCT AAGTCTCTCT CCTCTGTTTC
C  K  H  E   V  L  E   Q  G  K   V  V  M  D   S  E  R   G  D  K>

     4810      4820      4830      4840      4850      4860
   *    *    *    *    *    *    *    *    *    *    *    *
GTTATGGGTC AACAGGAGTA TTCTCCTCTT GGGTTGACAG GATTGAGGAA GCAGAAATAA
CAATACCCAG TTGTCCTCAT AAGAGGAGAA CCCAACTGTC CTAACTCCTT CGTCTTTATT
G  Y  G  S   T  G  V   F  S  S   W  V  D  R   I  E  E   A  E  I>

     4870      4880      4890      4900      4910      4920
   *    *    *    *    *    *    *    *    *    *    *    *
ATCATGAAAA ATTTCACTCA GATCCACAAT ACTTAAGGAC TGAATTTAAT TTACCCAAGA
TAGTACTTTT TAAAGTGAGT CTAGGTGTTA TGAATTCCTG ACTTAAATTA AATGGGTTCT
N  H  E  K   F  H  S   D  P  Q   Y  L  R  T   E  F  N   L  P  K>

     4930      4940      4950      4960      4970      4980
   *    *    *    *    *    *    *    *    *    *    *    *
TGGTTGCAGA AGAGATAAGA CGAAAGTGCC CTGTATGTAG AATCAGAGGA GAACAAGTGG
ACCAACGTCT TCTCTATTCT GCTTTCACGG GACATACATC TTAGTCTCCT CTTGTTCACC
M  V  A  E   E  I  R   R  K  C   P  V  C  R   I  R  G   E  Q  V>

     4990      5000      5010      5020      5030      5040
   *    *    *    *    *    *    *    *    *    *    *    *
GAGGACAATT GAAAATAGGG CCTGGAATAT GGCAAGTGGA TTGCACACAC TTTAATAGTA
CTCCTGTTAA CTTTTATCCC GGACCTTATA CCGTTCACCT AACGTGTGTG AAATTATCAT
G  G  Q  L   K  I  G   P  G  I   W  Q  V  D   C  T  H   F  N  S>

     5050      5060      5070      5080      5090      5100
   *    *    *    *    *    *    *    *    *    *    *    *
AGATAATCAT TGTAGCAGTA CATGTGGAAT CAGGATTTTT ATGGGCACAG ATAATTCCAC
TCTATTAGTA ACATCGTCAT GTACACCTTA GTCCTAAAAA TACCCGTGTC TATTAAGGTG
K  I  I  I   V  A  V   H  V  E   S  G  F  L   W  A  Q   I  I  P>
```

Figure 1, continued

```
      5110       5120       5130       5140       5150       5160
   *    *     *    *     *    *     *    *     *    *     *    *
AGGAGACTGC AGATTGTACA GTCAAGGCTC TTCTGCAACT TATATGTGCT CATAATGTTA
TCCTCTGACG TCTAACATGT CAGTTCCGAG AAGACGTTGA ATATACACGA GTATTACAAT
Q  E  T  A   D  C  T   V  K  A   L  L  Q  L   I  C  A   H  N  V>

      5170       5180       5190       5200       5210       5220
   *    *     *    *     *    *     *    *     *    *     *    *
CAGAATTACA AACAGACAAT GGACCAAATT TTAAAAATCA GAAAATGGAA GGTTTATTAA
GTCTTAATGT TTGTCTGTTA CCTGGTTTAA AATTTTTAGT CTTTTACCTT CCAAATAATT
T  E  L  Q   T  D  N   G  P  N   F  K  N  Q   K  M  E   G  L  L>

      5230       5240       5250       5260       5270       5280
   *    *     *    *     *    *     *    *     *    *     *    *
ATTTTATGGG AATAAAACAT AAATTAGGGA TACCAGGTAA CCCACAATCA CAGGCATTAG
TAAAATACCC TTATTTTGTA TTTAATCCCT ATGGTCCATT GGGTGTTAGT GTCCGTAATC
N  F  M  G   I  K  H   K  L  G   I  P  G  N   P  Q  S   Q  A  L>

      5290       5300       5310       5320       5330       5340
   *    *     *    *     *    *     *    *     *    *     *    *
TGGAAAATGC TAATAACACA TTAAAAGCTT GGATTCAAAA ATTCCTACCA GAGACTACCT
ACCTTTTACG ATTATTGTGT AATTTTCGAA CCTAAGTTTT TAAGGATGGT CTCTGATGGA
V  E  N  A   N  N  T   L  K  A   W  I  Q  K   F  L  P   E  T  T>

      5350       5360       5370       5380       5390       5400
   *    *     *    *     *    *     *    *     *    *     *    *
CTCTGGATAA TGCTCTGGCC CTAGCCCTGT ATAGTCTCAA CTTTAAACAA AGGGGTAGAC
GAGACCTATT ACGAGACCGG GATCGGGACA TATCAGAGTT GAAATTTGTT TCCCCATCTG
S  L  D  N   A  L  A   L  A  L   Y  S  L  N   F  K  Q   R  G  R>

      5410       5420       5430       5440       5450       5460
   *    *     *    *     *    *     *    *     *    *     *    *
TAGGAAGGAT GGCCCCTTAT GAATTATACA TACAACAAGA ATCATTAAGA ATACAAGACT
ATCCTTCCTA CCGGGGAATA CTTAATATGT ATGTTGTTCT TAGTAATTCT TATGTTCTGA
L  G  R  M   A  P  Y   E  L  Y   I  Q  Q  E   S  L  R   I  Q  D>

      5470       5480       5490       5500       5510       5520
   *    *     *    *     *    *     *    *     *    *     *    *
ATTTTTCGCA GATTCCACAA AAGTTAATGA TGCAGTGGGT GTATTACAAA GATCAAAAAG
TAAAAAGCGT CTAAGGTGTT TTCAATTACT ACGTCACCCA CATAATGTTT CTAGTTTTTC
Y  F  S  Q   I  P  Q   K  L  M   M  Q  W  V   Y  Y  K   D  Q  K>

      5530       5540       5550       5560       5570       5580
   *    *     *    *     *    *     *    *     *    *     *    *
ACAAAAAATG GAAGGGACCA ATGAGAGTGG AATATTGGGG ACAAGGATCA GTATTATTAA
TGTTTTTTAC CTTCCCTGGT TACTCTCACC TTATAACCCC TGTTCCTAGT CATAATAATT
D  K  K  W   K  G  P   M  R  V   E  Y  W  G   Q  G  S   V  L  L>
```

Figure 1, continued

```
      5590      5600      5610      5620      5630      5640
       *    *    *    *    *    *    *    *    *    *    *    *
AGGATGAAGA GAAGGGATAT TTTCTTGTAC CTAGGAGACA CATAAGAAGA GTCCCAGAAC
TCCTACTTCT CTTCCCTATA AAAGAACATG GATCCTCTGT GTATTCTTCT CAGGGTCTTG
K  D  E  E   K  G  Y   F  L  V   P  R  R  H   I  R  R   V  P  E>

      5650      5660      5670      5680      5690      5700
       *    *    *    *    *    *    *    *    *    *    *    *
CCTGCACTCT TCCTGAAGGG GATGAGTGAC GAAGATTGGC AGGTAAGTAG AAGACTCTTT
GGACGTGAGA AGGACTTCCC CTACTCACTG CTTCTAACCG TCCATTCATC TTCTGAGAAA
                        M  S  D   E  D  W   Q  V  S  R   R  L  F>
                 ORF 2 →
P  C  T  L   P  E  G   D  E>
                        ← ORF1

      5710      5720      5730      5740      5750      5760
       *    *    *    *    *    *    *    *    *    *    *    *
GCAGTGCTCC AAGGAGGAGT ACGTAGTGCT ATGCTATACA TATCTAGACT ACCTCCGGAC
CGTCACGAGG TTCCTCCTCA TGCATCACGA TACGATATGT ATAGATCTGA TGGAGGCCTG
A  V  L   Q  G  G  V   R  S  A   M  L  Y   I  S  R  L   P  P  D>

      5770      5780      5790      5800      5810      5820
       *    *    *    *    *    *    *    *    *    *    *    *
GAAAGAGAAA GGTATAAAAA AGACTTTAAG AAAAGGCTTT TGGAAAAGGA AACAGGATTC
CTTTCTCTTT CCATATTTTT TCTGAAATTC TTTTCCGAAA ACCTTTTCCT TTGTCCTAAG
E  R  E   R  Y  K  K   D  F  K   K  R  L   L  E  K  E   T  G  F>

      5830      5840      5850      5860      5870      5880
       *    *    *    *    *    *    *    *    *    *    *    *
ATACAGAGAT TAAGAAAAGC GGAAGGAATA AGGTGGAGCT TCCATACTAG AGATTATTAT
TATGTCTCTA ATTCTTTTCG CCTTCCTTAT TCCACCTCGA AGGTATGATC TCTAATAATA
I  Q  R   L  R  K  A   E  G  I   R  W  S   F  H  T  R   D  Y  Y>

      5890      5900      5910      5920      5930      5940
       *    *    *    *    *    *    *    *    *    *    *    *
ATAGGATATG TAAGAGAGAT GGTGGCCGGA TCTAGTCTAC CAGATAGTTT AAGACTGTAT
TATCCTATAC ATTCTCTCTA CCACCGGCCT AGATCAGATG GTCTATCAAA TTCTGACATA
I  G  Y   V  R  E  M   V  A  G   S  S  L   P  D  S  L   R  L  Y>

      5950      5960      5970      5980      5990      6000
       *    *    *    *    *    *    *    *    *    *    *    *
ATTTATATAA GCAATCCATT GTGGCACTGG TCATACCGTC CTGGCCTGAC AAATTTTAAT
TAAATATATT CGTTAGGTAA CACCGTGACC AGTATGGCAG GACCGGACTG TTTAAAATTA
I  Y  I   S  N  P  L   W  H  W   S  Y  R   P  G  L  T   N  F  N>
```

Figure 1, continued

```
      6010       6020       6030       6040       6050       6060
         *          *          *          *          *          *
ACAGAATGGC CTTTTGTGAA TATGTGGATA AAGACAGGAT TCATGTGGGA TGATATTGAA
TGTCTTACCG GAAAACACTT ATACACCTAT TTCTGTCCTA AGTACACCCT ACTATAACTT
 T  E  W   P  F  V  N   M  W  I   K  T  G   F  M  W  D   D  I  E>

      6070       6080       6090       6100       6110       6120
         *          *          *          *          *          *
AGCCAGAATA TTTGCAAAGG AGGAGAGATT TCACATGGAT GGGGACCTGG AATGGTGGGA
TCGGTCTTAT AAACGTTTCC TCCTCTCTAA AGTGTACCTA CCCCTGGACC TTACCACCCT
 S  Q  N   I  C  K  G   G  E  I   S  H  G   W  G  P  G   M  V  G>

      6130       6140       6150       6160       6170       6180
         *          *          *          *          *          *
ATTGTGATAA AAGCTTTTAG TTGTGGAGAA AGAAAGATTG AGGCTACTCC TGTAATGATT
TAACACTATT TTCGAAAATC AACACCTCTT TCTTTCTAAC TCCGATGAGG ACATTACTAA
 I  V  I   K  A  F  S   C  G  E   R  K  I   E  A  T  P   V  M  I>

      6190       6200       6210       6220       6230       6240
         *          *          *          *          *          *
ATAAGAGGAG AAATAGATCC AAAAAAATGG TGTGGAGATT GTTGGAATTT GATGTGTCTT
TATTCTCCTC TTTATCTAGG TTTTTTTACC ACACCTCTAA CAACCTTAAA CTACACAGAA
 I  R  G   E  I  D  P   K  K  W   C  G  D   C  W  N  L   M  C  L>

      6250       6260       6270       6280       6290       6300
         *          *          *          *          *          *
AGGAACTCAC CTCCACAGAC TTTACAAAGA CTTGCTATGT TGGCATGTGG CGTGCCGGCT
TCCTTGAGTG GAGGTGTCTG AAATGTTTCT GAACGATACA ACCGTACACC GCACGGCCGA
 R  N  S   P  P  Q  T   L  Q  R   L  A  M   L  A  C  G   V  P  A>

      6310       6320       6330       6340       6350       6360
         *          *          *          *          *          *
AAGGAGTGGC GAGGATGCTG TAATCAACGC TTTGTTTCTC CTTACAGAAC GCCTGCTGAT
TTCCTCACCG CTCCTACGAC ATTAGTTGCG AAACAAAGAG GAATGTCTTG CGGACGACTA
 K  E  W   R  G  C  C   N  Q  R   F  V  S   P  Y  R  T   P  A  D>

      6370       6380       6390       6400       6410       6420
         *          *          *          *          *          *
TTGGAGGTCA TTCAATCCAA GCCCAGCTGG AGTCTATTAT GGTCAGGGAG CCTATGAATG
AACCTCCAGT AAGTTAGGTT CGGGTCGACC TCAGATAATA CCAGTCCCTC GGATACTTAC
 L  E  V   I  Q  S  K   P  S  W   S  L  L   W  S  G  S   L>
                                                   ORF2 ←

      6430       6440       6450       6460       6470       6480
         *          *          *          *          *          *
GAAGACATAC TAACATTATT TAATAAGGTC ACTAAGAAAC TAGAAAAGGA AAAAGCTATC
CTTCTGTATG ATTGTAATAA ATTATTCCAG TGATTCTTTG ATCTTTTCCT TTTTCGATAG
```

Figure 1, continued

```
      6490       6500       6510       6520       6530       6540
    *    *     *    *     *    *     *    *     *    *     *    *
AGAATATTTG TATTAGCACA TCAATTAGAA AGGGACAAAG TTATTAGATT ACTACAAGGA
TCTTATAAAC ATAATCGTGT AGTTAATCTT TCCCTGTTTC AATAATCTAA TGATGTTCCT

      6550       6560       6570       6580       6590       6600
    *    *     *    *     *    *     *    *     *    *     *    *
TTAGTTTGGA GACATAGATT TAAGAAACCC CAAACAAAAT ACTGTTTATG TTGGTTCTGT
AATCAAACCT CTGTATCTAA ATTCTTTGGG GTTTGTTTTA TGACAAATAC AACCAAGACA

      6610       6620       6630       6640       6650       6660
    *    *     *    *     *    *     *    *     *    *     *    *
TGCAAATTCT ACTATTGGCA GTTGCAATCT ACATTATCAA TAACTACTGC TTAGAAATAC
ACGTTTAAGA TGATAACCGT CAACGTTAGA TGTAATAGTT ATTGATGACG AATCTTTATG

      6670       6680       6690       6700       6710       6720
    *    *     *    *     *    *     *    *     *    *     *    *
TTATAATAAT ATTTCATTTG CAACAATAAT TATGGCAGAA GGATTTGCAG CCAATAGACA
AATATTATTA TAAAGTAAAC GTTGTTATTA ATACCGTCTT CCTAAACGTC GGTTATCTGT
                                  M  A  E   G  F  A   A  N  R  Q>
                                 → ENV

      6730       6740       6750       6760       6770       6780
    *    *     *    *     *    *     *    *     *    *     *    *
ATGGATAGGA CCAGAAGAAG CTGAAGAGTT ATTAGATTTT GATATAGCAA CACAAATGAA
TACCTATCCT GGTCTTCTTC GACTTCTCAA TAATCTAAAA CTATATCGTT GTGTTTACTT
 W  I  G   P  E  E   A  E  E  L   L  D  F   D  I  A   T  Q  M  N>

      6790       6800       6810       6820       6830       6840
    *    *     *    *     *    *     *    *     *    *     *    *
TGAAGAAGGG CCACTAAATC CAGGGATGAA CCCATTTAGG GTACCTGGAA TAACAGATAA
ACTTCTTCCC GGTGATTTAG GTCCCTACTT GGGTAAATCC CATGGACCTT ATTGTCTATT
 E  E  E   P  L  N   P  G  M  N   P  F  R   V  P  G   I  T  D  K>

      6850       6860       6870       6880       6890       6900
    *    *     *    *     *    *     *    *     *    *     *    *
AGAAAAGCAA GACTATTGTA ACATATTACA ACCTAAGTTA CAAGATTTAC GGAATGAACT
TCTTTTCGTT CTGATAACAT TGTATAATGT TGGATTCAAT GTTCTAAATG CCTTACTTGA
 E  K  Q   D  Y  C   N  I  L  Q   P  K  L   Q  D  L   R  N  E  L>

      6910       6920       6930       6940       6950       6960
    *    *     *    *     *    *     *    *     *    *     *    *
TCAAGAGGTA AAACTAGAAG AAGGAAATGC AGGTAAGTTT AGAAGGGCAA GATATTTAAG
AGTTCTCCAT TTTGATCTTC TTCCTTTACG TCCATTCAAA TCTTCCCGTT CTATAAATTC
 Q  E  V   K  L  E   E  G  N  A   G  K  F   R  R  A   R  Y  L  R>
```

15/44

Figure 1, continued

```
      6970      6980      6990      7000      7010      7020
       *    *     *    *     *    *     *    *     *    *     *    *
ATATTCTGAT GAAAATGTGC TATCTATAGT CTATTTGCTA ATAGGATATC TAAGATATTT
TATAAGACTA CTTTTACACG ATAGATATCA GATAAACGAT TATCCTATAG ATTCTATAAA
  Y  S  D   E  N  V   L  S  I  V   Y  L  L   I  G  Y   L  R  Y  L>

      7030      7040      7050      7060      7070      7080
       *    *     *    *     *    *     *    *     *    *     *    *
AATAAATCGT AGGAGTTTAG GATCTTTAAG ACATGATATA GACATAGAAA CACCTCAAGA
TTATTTAGCA TCCTCAAATC CTAGAAATTC TGTACTATAT CTGTATCTTT GTGGAGTTCT
  I  N  R   R  S  L   G  S  L  R   H  D  I   D  I  E   T  P  Q  E>

      7090      7100      7110      7120      7130      7140
       *    *     *    *     *    *     *    *     *    *     *    *
GGAATATTAT AGTAATAGTG AAAGGGGTAC CACATTAAAT CAAAAATATG CGAGAAGATG
CCTTATAATA TCATTATCAC TTTCCCCATG GTGTAATTTA GTTTTTATAC GCTCTTCTAC
  E  Y  Y   S  N  S   E  R  G  T   T  L  N   Q  K  Y   A  R  R  C>

      7150      7160      7170      7180      7190      7200
       *    *     *    *     *    *     *    *     *    *     *    *
TTGTGTTAGC ACACTTATTA TGTATTTAAT TCTTTTTGCA GTAGGCATCT GGTGGGGAGC
AACACAATCG TGTGAATAAT ACATAAATTA AGAAAAACGT CATCCGTAGA CCACCCCTCG
  C  V  S   T  L  I   M  Y  L  I   L  F  A   V  G  I   W  W  G  A

      7210      7220      7230      7240      7250      7260
       *    *     *    *     *    *     *    *     *    *     *    *
TAGAGCACAA GTAGTGTGGA GACTTCCCCC TTTAGTAGTT CCAGTAGAAG AATCAGAAAT
ATCTCGTGTT CATCACACCT CTGAAGGGGG AAATCATCAA GGTCATCTTC TTAGTCTTTA
  R  A  Q   V  V  W   R  L  P  P   L  V  V   P  V  E   E  S  E  I>

      7270      7280      7290      7300      7310      7320
       *    *     *    *     *    *     *    *     *    *     *    *
AATTTTTTGG GATTGTTGGG CACCAGAAGA ACCCGCCTGT CAAGACTTTC TTGGGGCAAT
TTAAAAAACC CTAACAACCC GTGGTCTTCT TGGGCGGACA GTTCTGAAAG AACCCCGTTA
  I  F  W   D  C  W   A  P  E  E   P  A  C   Q  D  F   L  G  A  M>

      7330      7340      7350      7360      7370      7380
       *    *     *    *     *    *     *    *     *    *     *    *
GATACATCTA AAAGCTAGTA CGAATATAAG TATACAAGAG GGACCTACCT TGGGGAATTG
CTATGTAGAT TTTCGATCAT GCTTATATTC ATATGTTCTC CCTGGATGGA ACCCCTTAAC
  I  H  L   K  A  S   T  N  I  S   I  Q  E   G  P  T   L  G  N  W>

      7390      7400      7410      7420      7430      7440
       *    *     *    *     *    *     *    *     *    *     *    *
GGCTAGAGAA ATATGGGGAA CATTATTCAA AAAGGCTACC AGACAATGTA GAAGAGGTAG
CCGATCTCTT TATACCCCTT GTAATAAGTT TTTCCGATGG TCTGTTACAT CTTCTCCATC
  A  R  E   I  W  G   T  L  F  K   K  A  T   R  Q  C   R  R  G  R>
```

Figure 1, continued

```
        7450      7460      7470      7480      7490      7500
           *         *         *         *         *         *
AATATGGAAA AGATGGAATG AAACTATAAC AGGACCATTA GGATGTGCTA ATAACACATG
TTATACCTTT TCTACCTTAC TTTGATATTG TCCTGGTAAT CCTACACGAT TATTGTGTAC
 I  W  K   R  W  N   E  T  I  T   G  P  L   G  C  A   N  N  T  C>

        7510      7520      7530      7540      7550      7560
           *         *         *         *         *         *
TTATAATATT TCAGTAATAG TACCTGATTA TCAATGTTAT CTAGACCGAG TAGATACTTG
AATATTATAA AGTCATTATC ATGGACTAAT AGTTACAATA GATCTGGCTC ATCTATGAAC
 Y  N  I   S  V  I   V  P  D  Y   Q  C  Y   L  D  R   V  D  T  W>

        7570      7580      7590      7600      7610      7620
           *         *         *         *         *         *
GTTACAAGGG AAAGTAAATA TATCATTATG TCTAACAGGA GGAAAAATGT TGTACAATAA
CAATGTTCCC TTTCATTTAT ATAGTAATAC AGATTGTCCT CCTTTTTACA ACATGTTATT
 L  Q  G   K  V  N   I  S  L  C   L  T  G   G  K  M   L  Y  N  K>

        7630      7640      7650      7660      7670      7680
           *         *         *         *         *         *
ATATACAAAA CAATTAAGCT ATTGTACAGA CCCATTACAA ATCCCACTGA TCAATTATAC
TATATGTTTT GTTAATTCGA TAACATGTCT GGGTAATGTT TAGGGTGACT AGTTAATATG
 Y  T  K   Q  L  S   Y  C  T  D   P  L  Q   I  P  L   I  N  Y  T

        7690      7700      7710      7720      7730      7740
           *         *         *         *         *         *
ATTTGGACCT AATCAAACAT GTATGTGGAA CACTTCACAA ATTCAGGACC CTGAGATACC
TAAACCTGGA TTAGTTTGTA CATACACCTT GTGAAGTGTT TAAGTCCTGG GACTCTATGG
 F  G  P   N  Q  T   C  M  W  N   T  S  Q   I  Q  D   P  E  I  P>

        7750      7760      7770      7780      7790      7800
           *         *         *         *         *         *
AAAATGTGGA TGGTGGAATC AAAGAGCCTA TTATAAAAAT TGTAAATGGG AAAAAACAGA
TTTTACACCT ACCACCTTAG TTTCTCGGAT AATATTTTTA ACATTTACCC TTTTTTGTCT
 K  C  G   W  W  N   Q  R  A  Y   Y  K  N   C  K  W   E  K  T  D>

        7810      7820      7830      7840      7850      7860
           *         *         *         *         *         *
TGTAAAGTTT CATTGTCAAA GAACACAGAG TCAGCCTGGA ACATGGCTTA GAGCAATCTC
ACATTTCAAA GTAACAGTTT CTTGTGTCTC AGTCGGACCT TGTACCGAAT CTCGTTAGAG
 V  K  F   H  C  Q   R  T  Q  S   Q  P  G   T  W  L   R  A  I  S>

        7870      7880      7890      7900      7910      7920
           *         *         *         *         *         *
GTCATGGAGA CAAAGGAATA GATGGGAATG GAGACCAGAT TTTGAAAGTG AAAAGGTGAA
CAGTACCTCT GTTTCCTTAT CTACCCTTAC CTCTGGTCTA AAACTTTCAC TTTTCCACTT
 S  W  R   Q  R  N   R  W  E  W   R  P  D   F  E  S   E  K  V  K>
```

Figure 1, continued

```
      7930      7940      7950      7960      7970      7980
       *    *     *    *     *    *     *    *     *    *     *    *
AATATCTCTA AAGTGTAATA GCACAAAAAA CCTAACCTTT GCAATGAGAA GTTCAGGAGA
TTATAGAGAT TTCACATTAT CGTCTTTTTT GGATTGGAAA CGTTACTCTT CAAGTCCTCT
  I  S  L   K  C  N   S  T  K  N   L  T  F   A  M  R   S  S  G  D>

      7990      8000      8010      8020      8030      8040
       *    *     *    *     *    *     *    *     *    *     *    *
TTATGGAGAA GTAACGGGAG CTTGGATAGA GTTTGGATGT CATAGAAATA AATCAAAACT
AATACCTCTT CATTGCCCTC GAACCTATCT CAAACCTACA GTATCTTTAT TTAGTTTTGA
  Y  G  E   V  T  G   A  W  I  E   F  G  C   H  R  N   K  S  K  L>

      8050      8060      8070      8080      8090      8100
       *    *     *    *     *    *     *    *     *    *     *    *
TCATGATGAA GCAAGGTTTA GAATTAGATG TAGATGGAAT ATAGGGGAGA ATACCTCACT
AGTACTACTT CGTTCCAAAT CTTAATCTAC ATCTACCTTA TATCCCCTCT TATGGAGTGA
  H  D  E   A  R  F   R  I  R  C   R  W  N   I  G  E   N  T  S  L>

      8110      8120      8130      8140      8150      8160
       *    *     *    *     *    *     *    *     *    *     *    *
CATTGATACA TGTGGAAACA CTCAAAATGT TTCAGGGGCA AATCCTGTAG ATTGTACCAT
GTAACTATGT ACACCTTTGT GAGTTTTACA AAGTCCCCGT TTAGGACATC TAACATGGTA
  I  D  T   C  G  N   T  Q  N  V   S  G  A   N  P  V   D  C  T  M>

      8170      8180      8190      8200      8210      8220
       *    *     *    *     *    *     *    *     *    *     *    *
GTATGCAAAT AAAATGTACA ATTGTTCTTT ACAAAACGGG TTTACTATGA AGGTAGATGA
CATACGTTTA TTTTACATGT TAACAAGAAA TGTTTTGCCC AAATGATACT TCCATCTACT
  Y  A  N   K  M  Y   N  C  S  L   Q  N  G   F  T  M   K  V  D  D>

      8230      8240      8250      8260      8270      8280
       *    *     *    *     *    *     *    *     *    *     *    *
CCTTATTATG CATTTCAATA TGACAAAAGC TGTAGAAATG TATAATATTG CTGGAAATTG
GGAATAATAC GTAAAGTTAT ACTGTTTTCG ACATCTTTAC ATATTATAAC GACCTTTAAC
  L  I  M   H  F  N   M  T  K  A   V  E  M   Y  N  I   A  G  N  W>

      8290      8300      8310      8320      8330      8340
       *    *     *    *     *    *     *    *     *    *     *    *
GTCTTGTACA TCTGACTTGC CACCAACATG GGGGTATATG AATTGTAACT GTACAAATAA
CAGAACATGT AGACTGAACG GTGGTTGTAC CCCCATATAC TTAACATTGA CATGTTTATT
  S  C  T   S  D  L   P  P  T  W   G  Y  M   N  C  N   C  T  N  N>

      8350      8360      8370      8380      8390      8400
       *    *     *    *     *    *     *    *     *    *     *    *
TAGTAATGAT AATACTAGAA TGGCATGTCC TAACAATCAA GGCATCTTAA GGAATTGGTA
ATCATTACTA TTATGATCTT ACCGTACAGG ATTGTTAGTT CCGTAGAATT CCTTAACCAT
  S  N  D   N  T  R   M  A  C  P   N  N  Q   G  I  L   R  N  W  Y>
```

Figure 1, continued

```
     8410      8420      8430      8440      8450      8460
  *    *    *    *    *    *    *    *    *    *    *    *
TAACCCAGTA GCAGGATTAC GACAATCCTT GGAAAAGTAT CAAGTTGTAA AACAACCAGA
ATTGGGTCAT CGTCCTAATG CTGTTAGGAA CCTTTTCATA GTTCAACATT TTGTTGGTCT
 N  P  V   A  G  L   R  Q  S  L   E  K  Y   Q  V  V   K  Q  P  D>

     8470      8480      8490      8500      8510      8520
  *    *    *    *    *    *    *    *    *    *    *    *
TTACTTAGTG GTCCCAGGGG AAGTCATGGA ATATAAAACT AGAAGGAAAA GGGCAGCTAT
AATGAATCAC CAGGGTCCCC TTCAGTACCT TATATTTTGA TCTTCCTTTT CCCGTCGATA
 Y  L  V   V  P  G   E  V  M  E   Y  K  T   R  R  K   R  A  A  I>

     8530      8540      8550      8560      8570      8580
  *    *    *    *    *    *    *    *    *    *    *    *
TCATGTTATG TTAGCTCTTG CAACAGTATT ATCTATGGCC GGAGCAGGGA CGGGGGCTAC
AGTACAATAC AATCGAGAAC GTTGTCATAA TAGATACCGG CCTCGTCCCT GCCCCCGATG
 H  V  M   L  A  L   A  T  V  L   S  M  A   G  A  G   T  G  A  T>

     8590      8600      8610      8620      8630      8640
  *    *    *    *    *    *    *    *    *    *    *    *
TGCTATAGGG ATGGTAACAC AATATCACCA AGTTCTAGCA ACCCATCAAG AAGCTATTGA
ACGATATCCC TACCATTGTG TTATAGTGGT TCAAGATCGT TGGGTAGTTC TTCGATAACT
 A  I  G   M  V  T   Q  Y  H  Q   V  L  A   T  H  Q   E  A  I  E>

     8650      8660      8670      8680      8690      8700
  *    *    *    *    *    *    *    *    *    *    *    *
AAAGGTGACT GAAGCCTTAA AGATAAACAA CTTGAGATTA GTTACATTAG AGCATCAAGT
TTTCCACTGA CTTCGGAATT TCTATTTGTT GAACTCTAAT CAATGTAATC TCGTAGTTCA
 K  V  T   E  A  L   K  I  N  N   L  R  L   V  T  L   E  H  Q  V>

     8710      8720      8730      8740      8750      8760
  *    *    *    *    *    *    *    *    *    *    *    *
ACTAGTAATA GGATTAAAAG TAGAAGCTAT GGAAAAATTT TTATATACAG CTTTCGCTAT
TGATCATTAT CCTAATTTTC ATCTTCGATA CCTTTTTAAA AATATATGTC GAAAGCGATA
 L  V  I   G  L  K   V  E  A  M   E  K  F   L  Y  T   A  F  A  M>

     8770      8780      8790      8800      8810      8820
  *    *    *    *    *    *    *    *    *    *    *    *
GCAAGAATTA GGATGTAATC AAAATCAATT CTTCTGCAAA GTCCCTCCTG AATTGTGGAT
CGTTCTTAAT CCTACATTAG TTTTAGTTAA GAAGACGTTT CAGGGAGGAC TTAACACCTA
 Q  E  L   G  C  N   Q  N  Q  F   F  C  K   V  P  P   E  L  W  M>
        TM Peptide

     8830      8840      8850      8860      8870      8880
  *    *    *    *    *    *    *    *    *    *    *    *
GAGGTATAAT ATGTCTATAA ATCAAACAAT ATGGAATCAT GGAAATATAA CTTTGGGGGA
CTCCATATTA TACAGATATT TAGTTTGTTA TACCTTAGTA CCTTTATATT GAAACCCCCT
```

Figure 1, continued

```
R  Y  N   M  S  I   N  Q  T  I   W  N  H   G  N  I   T  L  G  E>

        8890       8900       8910       8920       8930       8940
           *          *          *          *          *          *
ATGGTATAAC CAAACAAAAG ATTTACAACA AAAGTTTTAT GAAATAATAA TGGACATAGA
TACCATATTG GTTTGTTTTC TAAATGTTGT TTTCAAAATA CTTTATTATT ACCTGTATCT
 W  Y  N   Q  T  K   D  L  Q  Q   K  F  Y   E  I  I   M  D  I  E>

        8950       8960       8970       8980       8990       9000
           *          *          *          *          *          *
ACAAAATAAT GTACAAGGGA AAAAAGGGAT ACAACAATTA CAAAAGTGGG AAGATTGGGT
TGTTTTATTA CATGTTCCCT TTTTTCCCTA TGTTGTTAAT GTTTTCACCC TTCTAACCCA
 Q  N  N   V  Q  G   K  K  G  I   Q  Q  L   Q  K  W   E  D  W  V>

        9010       9020       9030       9040       9050       9060
           *          *          *          *          *          *
AGGATGGATA GGAAATATTC CACAATACTT AAAGGGACTA TTGGGAGGTA TCTTGGGAAT
TCCTACCTAT CCTTTATAAG GTGTTATGAA TTTCCCTGAT AACCCTCCAT AGAACCCTTA
 G  W  I   G  N  I   P  Q  Y  L   K  G  L   L  G  G   I  L  G  I>

        9070       9080       9090       9100       9110       9120
           *          *          *          *          *          *
AGGATTAGGA GTGTTATTAT TAATTTTATG TTTACCCACA TTGGTTGATT GTATAAGAAA
TCCTAATCCT CACAATAATA ATTAAAATAC AAATGGGTGT AACCAACTAA CATATTCTTT
 G  L  G   V  L  L   L  I  L  C   L  P  T   L  V  D   C  I  R  N>

        9130       9140       9150       9160       9170       9180
           *          *          *          *          *          *
TTGTATCCAC AAGATACTAG GATACACAGT AATTGCAATG CCTGAAGTAG AAGGAGAAGA
AACATAGGTG TTCTATGATC CTATGTGTCA TTAACGTTAC GGACTTCATC TTCCTCTTCT
 C  I  H   K  I  L   G  Y  T  V   I  A  M   P  E  V   E  G  E  E>

        9190       9200       9210       9220       9230       9240
           *          *          *          *          *          *
AATACAACCA CAAATGGAAT TGAGGAGAAA TGGTAGGCAA TGTGGCATAT CTGAAAAAGA
TTATGTTGGT GTTTACCTTA ACTCCTCTTT ACCATCCGTT ACACCGTATA GACTTTTTCT
 I  Q  P   Q  M  E   L  R  R  N   G  R  Q   C  G  I   S  E  K  E>

        9250       9260       9270       9280       9290       9300
           *          *          *          *          *          *
GGAGGAATGA TGAAGTATCT CAGACTTATT TTATAAGGGA GATGCTGTGC TGAGTTCTTC
CCTCCTTACT ACTTCATAGA GTCTGAATAA AATATTCCCT CTACGACACG ACTCAAGAAG
 E  E>
  ← ENV

        9310       9320       9330       9340       9350       9360
           *          *          *          *          *          *
```

Figure 1, continued

```
CCTTTGAGGA AGGTATGTCA TATGAATCCA TTTCAAATCA AATTAAACTA ATAAAGTATG
GGAAACTCCT TCCATACAGT ATACTTAGGT AAAGTTTAGT TTAATTTGAT TATTTCATAC

      9370      9380      9390      9400      9410      9420
   *    *    *    *    *    *    *    *    *    *    *    *
TATTATAAGG TAAAAAGAAA AAAAGACAAA GAAGAAGAAG AAGGAAGAAA GCCTTCAAGA
ATAATATTCC ATTTTTCTTT TTTTCTGTTT CTTCTTCTTC TTCCTTCTTT CGGAAGTTCT

      9430      9440      9450      9460      9470      9480
   *    *    *    *    *    *    *    *    *    *    *    *
ATATGATGAC AGCTTTAGAA GATCGCTTTA GAAAGCTATT TGGCACAAAT TCTACAACGG
TATACTACTG TCGAAATCTT CTAGCGAAAT CTTTCGATAA ACCGTGTTTA AGATGTTGCC

      9490      9500      9510      9520      9530      9540
   *    *    *    *    *    *    *    *    *    *    *    *
GAGACAGTAC AGTGGAATCT GACGATGAAC CTCCTAAAAA AGAAAAAAGG GTGGACTGGG
CTCTGTCATG TCACCTTAGA CTGCTACTTG GAGGATTTTT TCTTTTTTCC CACCTGACCC

      9550      9560      9570      9580      9590      9600
   *    *    *    *    *    *    *    *    *    *    *    *
ATGAGTATTG GGACCCTGAA GAAATAGAAA GAATGCTTAT GGACTAGTGA CTGTTTACGA
TACTCATAAC CCTGGGACTT CTTTATCTTT CTTACGAATA CCTGATCACT GACAAATGCT

      9610      9620      9630      9640      9650      9660
   *    *    *    *    *    *    *    *    *    *    *    *
ACAAATGATA AATGATGGAA ACAGCTGAGC ATGACTCATA GTTAAAGCGC TAGCAGCTGC
TGTTTACTAT TTACTACCTT TGTCGACTCG TACTGAGTAT CAATTTCGCG ATCGTCGACG

      9670      9680      9690      9700      9710      9720
   *    *    *    *    *    *    *    *    *    *    *    *
TTAACCGCAA AACCACATCC TATGTAAAGC TTGCTGATGA CGTATAATTT GCTCCACTGT
AATTGGCGTT TTGGTGTAGG ATACATTTCG AACGACTACT GCATATTAAA CGAGGTGACA

      9730      9740      9750      9760      9770      9780
   *    *    *    *    *    *    *    *    *    *    *    *
AAAAGTATAT AACCAGTGCT TTGTGAGACT TCGGGGAGTC TCTCCGTTGA GGACTTTCGA
TTTTCATATA TTGGTCACGA AACACTCTGA AGCCCCTCAG AGAGGCAACT CCTGAAAGCT

      9790      9800      9810      9820      9830      9840
   *    *    *    *    *    *    *    *    *    *    *    *
GTTCTCCCTT GAGGCTCCCA CAGATACAAT AAATATTTGA GATTGAACCC TGTCAAGTAT
CAAGAGGGAA CTCCGAGGGT GTCTATGTTA TTTATAAACT CTAACTTGGG ACAGTTCATA

      9850      9860      9870      9880      9890
   *    *    *    *    *    *    *    *    *    *
CTGTGTAATC TTTTTTACCT GTGAGGTCTC GGAATCCGGG CCGAGAACTT CGCA
GACACATTAG AAAAAATGGA CACTCCAGAG CCTTAGGCCC GGCTCTTGAA GCGT
```

FIG. 2

Alignment of Gag Open Reading Frames of FIV Strains

FIG. 2A

```
                       10         20         30         40         50         60
FIV-NCSU Gag            *          *          *          *          *          *
               MGNGQGRDWK MAIKRCSNVA VGVGGKSKKF GEGNFRWAIR MANVSTGREP GDIPETLDQL
 1. FIV PPR             |          |          |          |          |          | 60
 [2141]        .......... .......... .......... .......... .......... ..........>
 2. FIV Z1              |          |          |          |          |          | 60
 [2138]        .......... .......... .......... .......... .......... ..........>
 3. FIV CG              |          |          |          |          |          | 60
 [2136]        .......... .......... .......... .......... .......... ..........>
 4. FIV 14              |          |          |          |          |          | 60
 [2132]        .......... .......... .......... .......... .......... ..........>
 5. FIV TM1             |          |          |          |          |          | 60
 [2012]        .......... .......... .....S...R .......... ....T..... .......E..>
 6. FIV TM2             |          |          |          |          |          | 60
 [2012]        .......... .......... .....S...R .......... ....T..... .......E..>
```

22/44

FIG. 2B

```
                  70         80         90         100        110        120
                   *          *          *          *          *          *
FIV-NCSU g    RLVICDLQER REKFGSSKEI DMAIVTLKVF AVVGLLNMTV STAAAAENMY TQMGLDTRPS
1. FIV PPR
[ 2141 ]      .......... .......... ...T...... .......... .......... .......... 120 >
2. FIV Z1
[ 2138 ]      .......... .......... .......... .A........ .......... S......... 120 >
3. FIV CG
[ 2136 ]      .......... .......... .......... .A........ .......... S......... 120 >
4. FIV 14
[ 2132 ]      .......... .......... .......... .A........ .......... S......... 120 >
5. FIV TM1
[ 2012 ]      SI.......D .HY....... ...T...... .A.I...... ...T...... A......... 120 >
6. FIV TM2
[ 2012 ]      SI.......D .HY....... ...T...... .A.I...... ...T...... A......... 120 >
```

FIG. 2C

```
                         130        140        150        160        170        180
FIV-NCSU g                 *          *          *          *          *          *
            MREAGGKEES PPQASPIQTA NGAPQYVALD PKMVSIFMEK AREGLGGEEV QLWFTAFSAN
                                                                              |
1.  FIV PPR                                                                  180
[ 2141 ]                                                                        >
            TK.......G ....Y....V .......... .......... .......... ..........
                                                                              |
2.  FIV Z1                                                                   180
[ 2138 ]                                                                        >
            .K.......G ....Y....V ..V....... .......... .......... ..........
                                                                              |
3.  FIV CG                                                                   180
[ 2136 ]                                                                        >
            .K.......G ....Y....V ..V....... .......... .......... ..........
                                                                              |
4.  FIV 14                                                                   180
[ 2132 ]                                                                        >
            .K.......G ....Y....V ..V....... .......... .......... ..........
                                                                              |
5.  FIV TM1                                                                  180
[ 2012 ]                                                                        >
            VK.S.....G ....Y....V .......... .......... .......... ..........
                                                                              |
6.  FIV TM2                                                                  180
[ 2012 ]                                                                        >
            VK.S.....G ....Y....V .......... .......... .......... ..........
```

FIG. 2D

```
                        190          200          210          220          230          240
                          *            *            *            *            *            *
FIV-NCSU g
                 LTPTDMATLI   MAAPGCAADK   EILDESLKQL   TAEYDRTHPP   DGPRPLPYFT   AAEIMGIGLT
1. FIV PPR                |            |            |            |            |            |
[ 2141 ]         ..........   ..........   ..........   .......N..   ..........   ..........240>
2. FIV Z1                 |            |            |            |            |            |
[ 2138 ]         ..........   ..........   ..........   ..........   A.........   ..........240>
3. FIV CG                 |            |            |            |            |            |
[ 2136 ]         ..........   ..........   ..........   ..........   A.........   ..........240>
4. FIV 14                 |            |            |            |            |            |
[ 2132 ]         ..........   ..........   ..........   ..........   A.........   ..........240>
5. FIV TM1                |            |            |            |            |            |
[ 2012 ]         S.........   S.........   .....T...M   ..........   ..........   ..........240>
6. FIV TM2                |            |            |            |            |            |
[ 2012 ]         S.........   S.........   .....T...M   ..........   ..........   ..........240>
```

FIG. 2E

```
                   250         260         270         280         290         300
                     *           *           *           *           *           *
FIV-NCSU g    QEQQAEARFA  PARMQCRAWY  LEALGKLAAI  KAKSPRAVQL  RQGAKEDYSS  FIDRLFAQID  300
1. FIV PPR
[2141]        ..........  ..........  ..........  ..........  ..........  ..........> 300
2. FIV Z1
[2138]        ..........  ..........  ..........  ..........  ..........  ..........> 300
3. FIV CG
[2136]        ..........  ..........  ..........  ..........  ..........  ..........> 300
4. FIV 14
[2132]        ..........  ..........  ..........  ..........  ..........  ..........> 300
5. FIV TM1
[2012]        .......P..  ..........  ..........  ..........  K.........  ..........> 300
6. FIV TM2
[2012]        .......P..  ..........  ..........  ..........  K.........  ..........> 300
```

FIG. 2F

```
                    310        320        330        340        350        360
                      *          *          *          *          *          *
FIV-NCSU g    QEQNTAEVKL YLKQSLSMAN ANAECKKAMS HLKPESTLEE KLRACQEVGS PGYKMQLLAE
1. FIV PPR
[ 2141 ]      .......... .......I.. .......... .......... .......I.. ..........> 360
2. FIV Z1
[ 2138 ]      .......... .......I.. ...D...... .......... .......I.. ..........> 360
3. FIV CG
[ 2136 ]      .......... .......I.. ...D...... .......... .......I.. ..........> 360
4. FIV 14
[ 2132 ]      .......... .......I.. ...D...... .......... .......I.. ..........> 360
5. FIV TM1
[ 2012 ]      .......... .......I.. ..PD..R... .......... .......... ..........> 360
6. FIV TM2
[ 2012 ]      .......... .......I.. ..PD..R... .......... .......... ..........> 360
```

FIG. 2G

```
                    370        380        390        400        410        420
                      *          *          *          *          *          *
FIV-NCSU g    ALTKVQVVQS KGSGPVCFNC KKPGHLAKQC RDVKKCNKCG KPGHLAAKCW QGGKKNSGNW
1. FIV PPR
[ 2141 ]      .......... .......... ........R. .......... .......... ....R.....>   420
2. FIV Z1
[ 2138 ]      .......... .......... ........R. .E........ .......... ..NR......>   420
3. FIV CG
[ 2136 ]      .......... .......... ........R. .E........ .......... ..NR......>   420
4. FIV 14
[ 2132 ]      .......... .......... ........R. .E........ .....V.... ..NR......>   420
5. FIV TM1
[ 2012 ]      ...R..T..T ..PRL..... ........R. KEA.R..N.. ........N. ...R.T...E>   420
6. FIV TM2
[ 2012 ]      ...R..T..T ..PRL..... ........R. KEA.R..N.. ........N. ...R.T...E>   420
```

FIG. 2H

```
                        430         440         450
FIV-NCSU g                *           *           *
                 KAGRAAAPVN  QVQQAVMPSA  PPMEERLLDL
 1. FIV PPR               |           |           |
[ 2141 ]                  |           |           |
            ................T............K....>
 2. FIV Z1                |           |           |
[ 2138 ]                  |           |           |
            .........................K....>
 3. FIV CG                |           |           |
[ 2136 ]                  |           |           |
            ............M..............K....>
 4. FIV 14                |           |           |
[ 2132 ]                  |           |           |
            ............M..............K....>
 5. FIV TM1               |           |           |
[ 2012 ]                  |           |           |
            .V..............-IV..........K....>
 6. FIV TM2               |           |           |
[ 2012 ]                  |           |           |
            .V..............-IV..........K....>
```

FIG. 3A

Alignment of Whole Envelope Protein Sequence

```
                       10         20         30         40         50         60
env-NCSU        *    *    *    *    *    *    *    *    *    *    *    *
             MAEGFAANRQ WIGPEEAEEL LDFDIATQMN EEGPLNPGMN PFRVPGITDK EKQDYCNILQ
1.  FIV 14
[ 4221 ]     ...........L.................S.........V.........E...N......>  60
2.  FIV Z1
[ 4202 ]     .............................S.........V.........E...N......>  60
3.  FIV CG
[ 4187 ]     .............................S.........V.........E...N......>  60
4.  fiv19k
[ 4168 ]     .....V..G....................L.........I.........Q...E...T..>  60
5.  FIV PPR
[ 4102 ]     .......................K...............V...AV.EA..D..E..K...>  60
```

FIG. 3B

```
                 70         80         90         100        110        120
env-NCSU 2   *    *    *    *    *    *    *    *    *    *    *    *
            PKLQDLRNEL QEVKLEEGNA GKFRRARYLR YSDENVLSIV YLLIGYLRYL INRRSLGSLR

1. FIV 14                                                              120
[ 4221 ]    .........I ..........  .......F.. ....S...L. HAF...CI.. G..NK.....>

2. FIV Z1                                                              120
[ 4202 ]    .......D.I ..........  .....T.F.. ....H...L. HAF...CI.. G..NK.....>

3. FIV CG                                                              120
[ 4187 ]    .........I ..........  .......F.. ....R...L. HAF...CI.. G..NK.....>

4. fiv19k                                                              120
[ 4168 ]    ....A....I .........R  .......F.. ....TI..LI .SFV..F... VD.KKF....>

5. FIV PPR                                                             120
[ 4102 ]    .R..EI...I ..........  .......F.. ....SI..LI H.F...CT.. V..R......>
```

FIG. 3C

```
                        *     130        *     140        *     150        *     160        *     170        *     180
env-NCSU 2                      *              *              *              *              *              *
            HDIDIETPQE      EYYSNSERGT     TLNQKYARRC     CVSTLIMYLI     LFAVGIWWGA     RAQVVWRLPP

                                                                           I        Q
1. FIV 14                                                                                          180
[ 4221 ]  .......A.....C.N.R.K..D.I..G....LG.VTL.....GII.YSTTN..........>

                                                                           I        Q
2. FIV Z1                                                                                          180
[ 4202 ]  ......A.......N.R.K..D.I..G....LG.VTL.....G.IVYST.G..........>

                                                                           T        Q
3. FIV CG                                                                                          180
[ 4187 ]  ......A....C.N.R.K...D.I..G....LG.VTL.....G.IVYST.G..........>

                                                                          AI
4.   fiv19k                                                                                        180
[ 4168 ]  .......A.......N.K.K.M.D.V..GK.L.G.AAF..L.IGII.IRTVD..........>

                                                                           I         T
5. FIV PPR                                                                                         180
[ 4102 ]  ...N..A....Q..SR.Q...E.I..G...LIG.ASL..L..G.A.Y L.TN..I.......>
```

FIG. 3D

```
                       190        200        210        220        230        240
env-NCSU 2       *    *    *    *    *    *    *    *    *    *    *    *
             LVVPVEESEI IFWDCWAPEE PACQDFLGAM IHLKASTNIS IQEGPTLGNW AREIWGTLFK
1.  FIV 14                                                              240
[ 4221 ]     .......... .......... .......... ....K..... R......... ....A.....>
2.  FIV Z1                                                              240
[ 4202 ]     .......... .........D .......... ....K..... R......... ....A.....>
3.  FIV CG                                                              240
[ 4187 ]     .......... .......... .......... ....K..... R......... ....A.....>
4.  fiv19k                                                              240
[ 4168 ]     .......... .......... .......... .......... .......... ....A.....>
5.  FIV PPR                                                             240
[ 4102 ]     .......... .......... .......... .......... .......... ..........>
```

FIG. 3E

```
                   *  250      *  260      *  270      *  280      *  290      *  300
env-NCSU 2     KATRQCRRGR IWKRWNETIT GPLGCANNTC YNISVIVPDY QCYLDRVDTW LQGKVNISLC

1. FIV 14                                                                      300
[ 4221 ]       .......... .......... ..S....... ..V....... .......... .....I.... >

2. FIV Z1                                                                      300
[ 4202 ]       .......... .......... ..S....... ..V....... .......... .....I.... >

3. FIV CG                                                                      300
[ 4187 ]       .......... .......... ..S....... ..V....... .......... .....I.... >

4. fiv19k                                                                      300
[ 4168 ]       .......... .......... ..I....... ......I... ...I...... ........I. >

5. FIV PPR                                                                     300
[ 4102 ]       ....H...NK .......... ..V....... ......I... .......... .......... >
```

FIG. 3F

```
                      310        320          330       340       350       360
env-NCSU 2         *   *      *   *        *   *      *   *      *   *     *   *
           LTGGKMLYNK YTKQLSYCTD PLQIPLINYT FGPNQTCMWN TSQIQDPEIP KCGWWNQRAY
1.  FIV 14                                                                 360
[ 4221 ]   .........V ..........  .......... .......... .......... .........M .>
2.  FIV Z1                                                                 360
[ 4202 ]   .........V ..........  .......... .......... .......... .........M .>
3.  FIV CG                                                                 360
[ 4187 ]   .........V ..........  .......... .......... .......... .........M .>
4.  fiv19k                                                                 360
[ 4168 ]   .........E ..........  .......... ..Q....... .......... .........K .>
5.  FIV PPR                                                                360
[ 4102 ]   ........RD ..........  .......... .......... .......... .........I .>
```

FIG. 3G

```
                             370            380              390           400            410            420
env-NCSU 2  *       *      *      *       *      *      *      *      *      *      *      *
          YKNCKWEKTD  VKFHCQRTQS  QPGTWLRAIS  SWRQRNRWEW  RPDFESEKVK  ISLKCNSTKN
1. FIV 14                                                                                    420
[ 4221 ] .NS....EAK..........S.F......K...........K......Q......>
2. FIV Z1                                                                                    420
[ 4202 ] .NR....EAK..........S.R......K.......L.........Q...K..>
3. FIV CG                                                                                    420
[ 4187 ] .NS....EAK..........S.F......K..........K.K......P......>
4. fiv19k                                                                                    420
[ 4168 ] .NQ.S..Q....Q..........S.I.....................R..V..Q....Q.>
5. FIV PPR                                                                                   420
[ 4102 ] .NS.R..S.N...Y...........I.T.......K....................Q....H.>
```

FIG. 3H

```
                    430        440        450        460        470        480
env-NCSU 2        *    *     *    *     *    *     *    *     *    *     *    *
                 LTFAMRSSGD YGEVTGAWIE FGCHRNKSKL HDEARFRIRC RWNIGENTSL IDTCGNTQNV
1. FIV 14                                                                  480
[ 4221 ]         .......... .......... .......... .A........ ...V.S.... ........K. >
2. FIV Z1                                                                  480
[ 4202 ]         .......... .......... .........H .S........ ...V.S.... ........D. >
3. FIV CG                                                                  480
[ 4187 ]         .......... .......... .........N .T........ ...V.SD... .......P.. >
4. fiv19k                                                                  480
[ 4168 ]         ...I...... .......... .........H .......... ...E.N.N.. .....K.... >
5. FIV PPR                                                                 480
[ 4102 ]         ....M..... .......... ........RF .T........ ...V.D.... .....KNL.. >
```

FIG. 3I

```
                     490        500        510        520        530        540
env-NCSU 2     *      *     *     *     *     *     *     *     *     *     *     *
          SGANPVDCTM YANKMYNCSL QNGFTMKVDD LIMHFNMTKA VEMYNIAGNW SCTSDLPPTW
1. FIV 14                                                             540
[ 4221 ]  .......... S......... .......... ......K... .......... ........SS>
2. FIV Z1                                                             540
[ 4202 ]  .......... S......... .......... .V..S..... K......... ........SS>
3. FIV CG                                                             540
[ 4187 ]  .......... S......... .......... .V........ .......... ........SS>
4. fiv19k                                                             540
[ 4168 ]  .......... ..R....... D......... .......... .......... ...M....TN>
5. FIV PPR                                                            540
[ 4102 ]  .......... .......... .......... .......... .......... ...K....QN>
```

FIG. 3J

```
                     *      550        *      560        *      570        *      580        *      590        *      600
env-NCSU 2                    *               *                 *                 *                 *                 *
             GYMNCNCTNN  SNDNTRMACP  NNQGILRNWY  NPVAGLRQSL  EKYQVVKQPD  YLVVPGEVME

1. FIV 14                      YS
[ 4221 ]                        I
                                I                                                    600
             .........S.SSG.K....S.R...................Q.....................E....>

2. FIV Z1                      YS
[ 4202 ]                        I
                                I                                                    600
             .........S.SSG.K....S.R...................Q.....................E....>

3. 6FIV CG                     YS
[ 4187 ]                        I
                                I                                                    600
             .........S.SSG.K....S.R...................Q..................L..E....>

4. fiv19k                        YT
[ 4168 ]                          I
                                  I                                                  600
             ...K.....DTSK.IK.E..EEK.......................................................>

5. FIV PPR                                                                           600
[ 4102 ]
             .........GTSNDNK....EDK...................A.............E.I..T....T>
```

FIG. 3K

```
                  610        620        630        640        650        660
env-NCSU 2      *    *     *    *     *    *     *    *     *    *     *    *
            YKTRRKRAAI HVMLALATVL SMAGAGTGAT AIGMVTQYHQ VLATHQEAIE KVTEALKINN
1. FIV 14            |          |          |          |          |          |
[ 4221 ]             |          |          |          |          |   660    |
            ..P........ ......A...I.......... .......... ........V. ..........>
2. FIV Z1            |          |          |          |          |          |
[ 4202 ]             |          |          |          |          |   660    |
            ..P........ ..........I.......... .......... .......... ..........>
3. FIV CG            |          |          |          |          |          |
[ 4187 ]             |          |          |          |          |   660    |
            ..P........ ..........I.......... .......... .......... ...G......>
4. fiv19k            |          |          |          |          |          |
[ 4168 ]             |          |          |          |          |          |
            ..P........ .......... .......... .......... .......... ...660...>
5. FIV PPR           |          |          |          |          |          |
[ 4102 ]             |          |          |          |          |    660   |
            ..YKQ.......I.........I.......... .........Q ........LD.I........>
```

FIG. 3L

```
                    670         680         690         700         710         720
                 *    *      *    *      *    *      *    *      *    *      *    *
env-NCSU 2    LRLVTLEHQV  LVIGLKVEAM  EKFLYTAFAM  QELGCNQNQF  FCKVPPELWM  RYNMSINQTI

1. FIV 14
[ 4221 ]      ..........  ..........  ..........  ..........  ..I......T  ...T......>
2. FIV Z1
[ 4202 ]      ..........  ..........  ..........  ..........  ..I...G..T  ...T......>
3. FIV CG
[ 4187 ]      ..........  ..........  ..........  ..........  ..I..L...T  ...T......>
4. fiv19k
[ 4168 ]      ..........  .........I  ..........  ..........  .....L...R  ...T......>
5. FIV PPR
[ 4102 ]      .........M  .........I  ..........  ..........  ..EI.K...L  ....TL....>
```

FIG. 3M

```
                      730         740         750         760         770         780
                   *    *      *    *      *    *      *    *      *    *      *    *
env-NCSU 2   WNHGNITLGE  WYNQTKDLQQ  KFYEIIMDIE  QNNVQGKKGI  QQLQKWEDWV  GWIGNIPQYL
1. FIV 14                                                                      780
[ 4221 ]     ..........  ..........  ..........  ..........  ..........  .......... >
2. FIV Z1                                                                      780
[ 4202 ]     ..........  ...K......  ..........  ........T.  ..........  .......... >
3. FIV CG                                                                      780
[ 4187 ]     ..........  ..........  ..........  ........T.  ..........  R......... >
4. fiv19k                                                                      780
[ 4168 ]     ..........  .........H  ..........  .........L  ..........  .......... >
5. FIV PPR                                                                     780
[ 4102 ]     ..........  .......Y..  ..........  ........QL  K..N.Q...M  ...K...... >
```

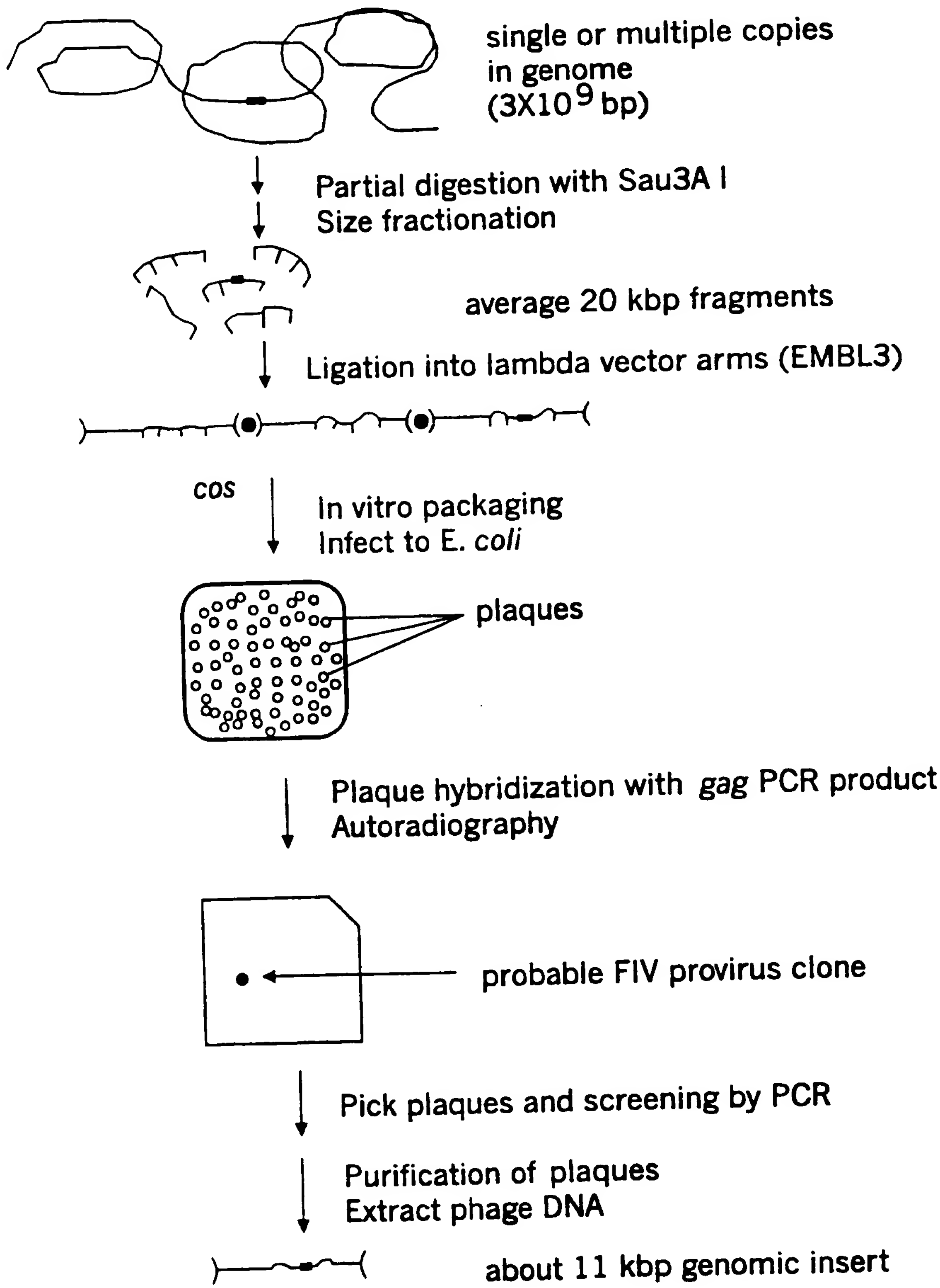
FIG. 3N

```
                    790         800         810         820         830         840
env-NCSU 2        *   *       *   *       *   *       *   *       *   *       *   *
             KGLLGGILGI  GLGVLLLILC  LPTLVDCIRN  CIHKILGYTV  IAMPEVEGEE  IQPQMELRRN
1. FIV 14             |           |           |           |           |     840   |
[ 4221 ]  ......................................................................>
2. FIV Z1             |           |           |           |           |     840   |
[ 4202 ]  ......................................................................>
3. FIV CG             |           |           |           |           |     840   |
[ 4187 ]  ......................................................................>
4. fiv19k             |           |           |           |           |     840   |
[ 4168 ]  ...........I.............................................D.DE.............>
5. FIV PPR            |           |           |           |           |     840   |
[ 4102 ]  ...........I........................S.V..........IDD..ETV.....K>
```

FIG. 3O

```
                          850
env-NCSU 2          *       *
           GRQCGISEKE EE
 1.  FIV 14                |
[ 4221 ]                   |
           . . . . . M . . . . . . .>
 2.  FIV Z1                |
[ 4202 ]                   |
           . . . . . M . . . . . . .>
 3.  FIV CG                |
[ 4187 ]                   |
           . . . . . M . . . . . . .>
 4.   fiv19k               |
[ 4168 ]                   |
           . . . . . M . . . . . . .>
 5.  FIV PPR               |
[ 4102 ]                   |
           . . . . . M . . . . . . .>
```

FIG. 4


single or multiple copies
in genome
(3X10^{9} bp)
Partial digestion with Sau3A I
Size fractionation
average 20 kbp fragments
Ligation into lambda vector arms (EMBL3)
cos
In vitro packaging
Infect to E. *coli*
plaques
Plaque hybridization with *gag* PCR product
Autoradiography
probable FIV provirus clone
Pick plaques and screening by PCR
Purification of plaques
Extract phage DNA
about 11 kbp genomic insert

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/04147

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/49 C12N15/73 C12N15/86 C12N7/00 C12N5/10
C12N1/19 C12N1/21 C07K14/155 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOO-SUNG YANG ET AL: "MOLECULARLY CLONED FELINE IMMUNODEFICIENCY VIRUS NCSU1 JSY3 INDUCES IMMUNODEFICIENCY IN SPECIFIC-PATHOGEN-FREE CATS" JOURNAL OF VIROLOGY, vol. 70, no. 5, May 1996, pages 3011-3017, XP000605486 see abstract see page 3012 see page 3016, column 2, paragraph 2	1-9,11, 12,19-21
Y		10,13-18

Y	WO 95 05460 A (UNIV NORTH CAROLINA ;TOMPKINS WAYNE A F (US); TOMPKINS MARY B (US)) 23 February 1995 see abstract see claims 1-11	10,13-18

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Date of the actual completion of the international search	Date of mailing of the international search report
17 June 1998	24/06/1998
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Galli, I

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte… …ional Application No
PCT/US 98/04147

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 7514594 A	14-03-1995
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